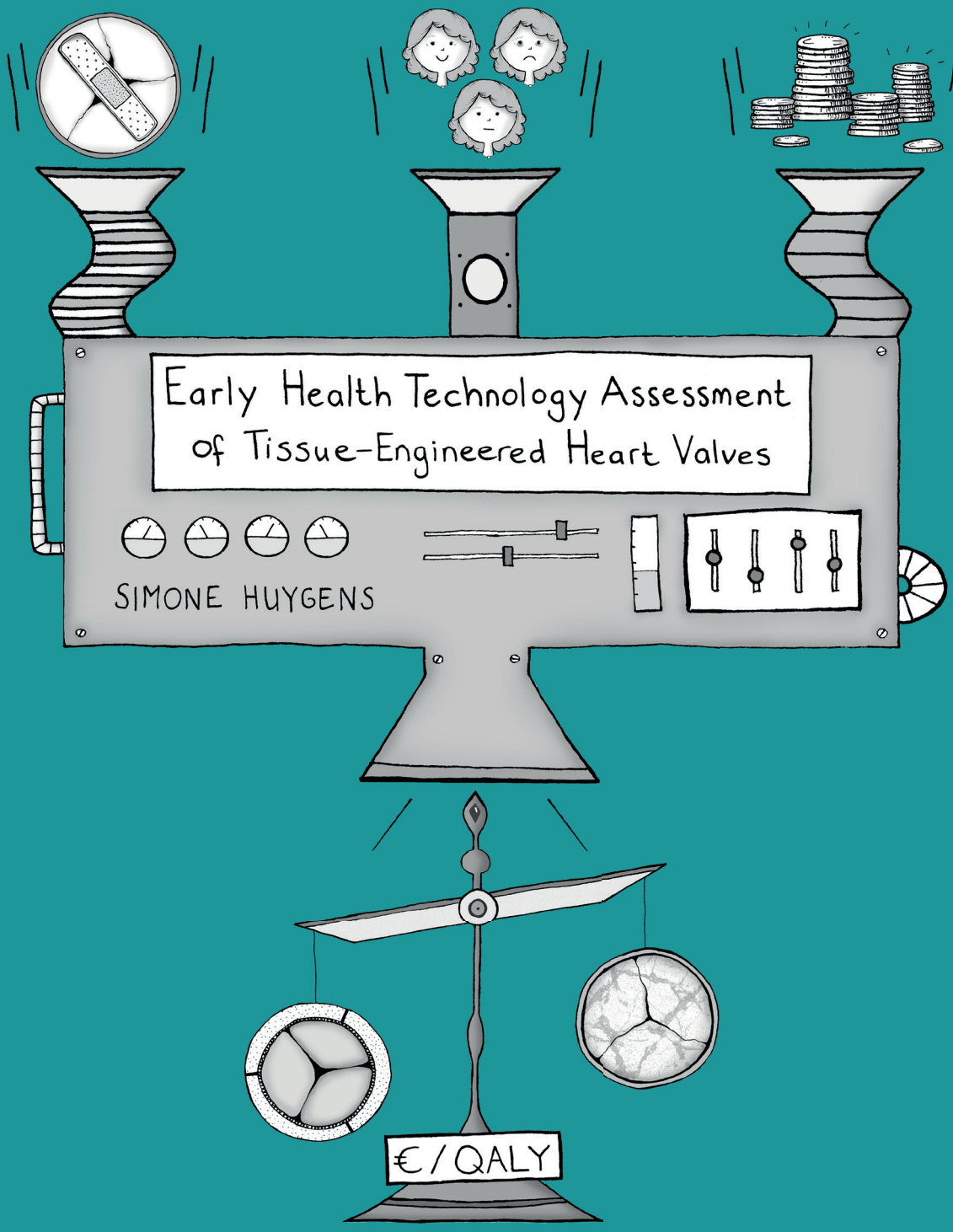
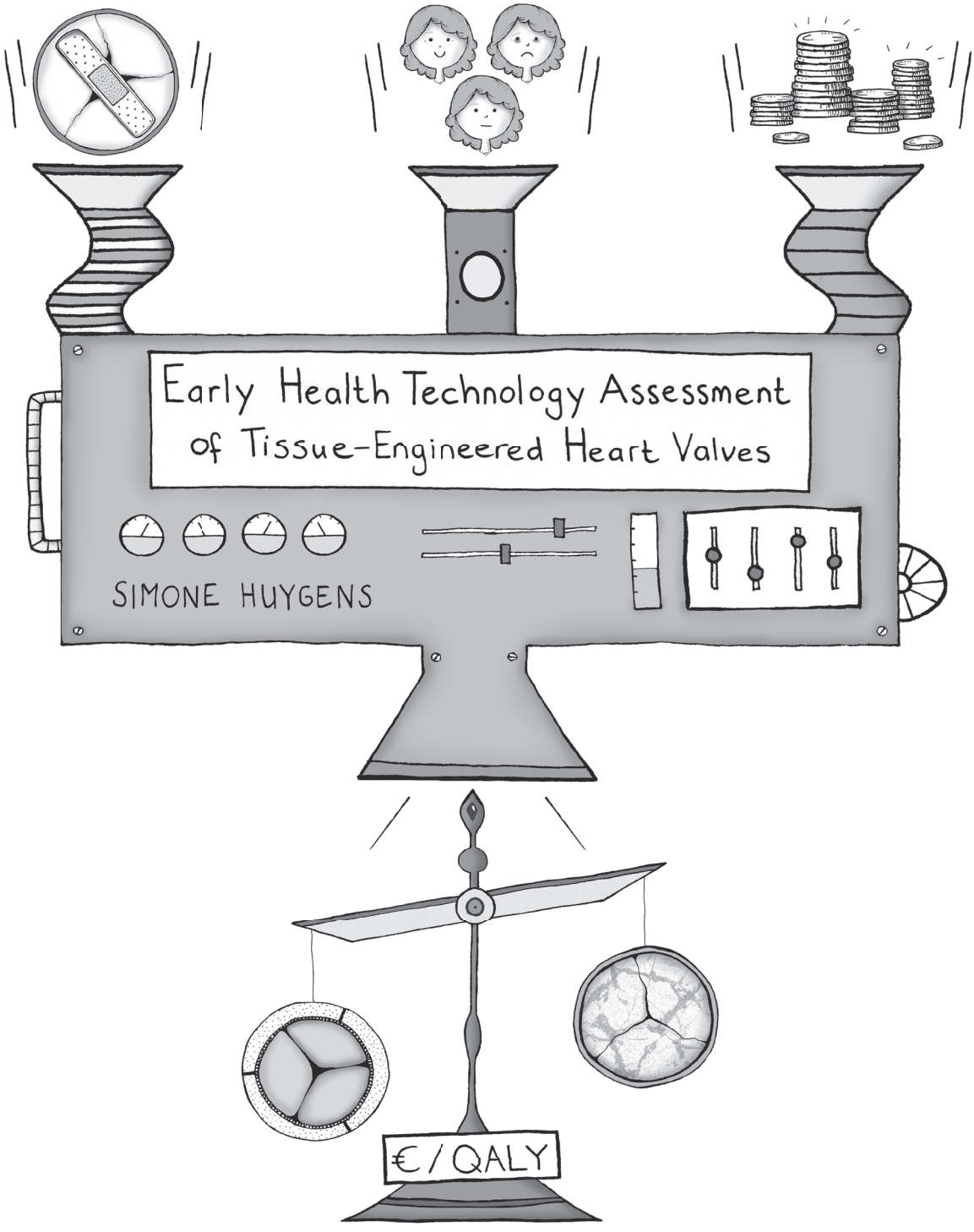

Early Health Technology Assessment of Tissue-Engineered Heart Valves
SIMONE HUYGENS
€/QALY


Early Health Technology Assessment
of Tissue-Engineered Heart Valves
SIMONE HUYGENS
€/QALY

Cover design: Pauline van Wingerden
Lay-out and printing: Proefschrift Maken / www.proefschriftmaken.nl

ISBN: 978-94-6380-217-8.

Early Health Technology Assessment of Tissue-Engineered Heart Valves

Vroege Health Technology Assessment van Tissue-Engineered Hartkleppen

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 20 februari 2019 om 13.30 uur

door

Simone Adriana Huygens
geboren te Zwijndrecht

Erasmus University Rotterdam

Erasmus

PROMOTIECOMMISSIE

Promotoren: Prof. dr. M.P.M.H. Rutten-van Mölken
Prof. dr. J.J.M. Takkenberg

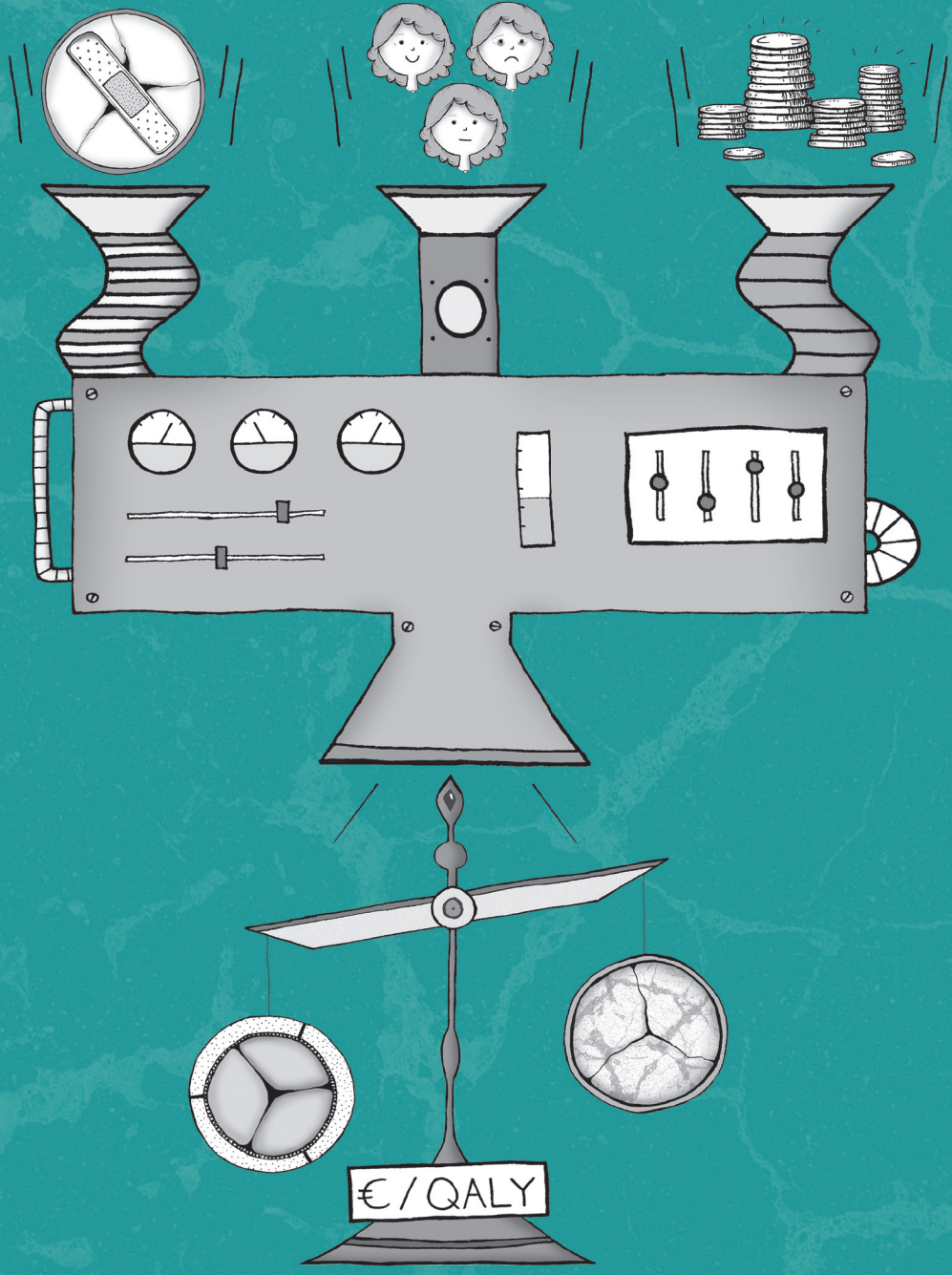
Overige leden: Dr. M.J. Al
Prof. dr. S.P. Hoerstrup
Prof. dr. mr. B.A.J.M. de Mol

Funded by Hartstichting

Financial support by the Dutch Heart Foundation and Erasmus University Medical Centre Rotterdam for the publication of this thesis is gratefully acknowledged.
The research described in this thesis was supported by a grant of the Dutch Heart Foundation (DHF 2012B001).

Voor mijn grootouders

CONTENTS


€ / QALY

1

General introduction

The development of the perfect heart valve substitute for patients with heart valve disease has not stood still since the implantation of the first artificial heart valve substitute in 1952.[1] One of the most promising recent endeavours is the construction of living valves through the process of tissue engineering.[2] Tissue-engineered heart valves (TEHV) have the potential to reduce or even eliminate the limitations of existing heart valve substitutes in patients who need heart valve replacement. This thesis describes the early Health Technology Assessment (HTA) of TEHV in the aortic position in elderly patients and in the pulmonary position in children. In this introduction heart valve disease, its causes, and current treatment options will be described, followed by an introduction to TEHV and their potential advantages compared to current treatment options. Subsequently, HTA will be introduced and a justification of the application of early HTA will be provided. Finally, the aim and outline of this thesis are described.

HEART VALVE DISEASE

Normal functioning heart valves allow blood to flow through the heart in one direction by opening and closing during the contractions of the heart (Figure 1).[3] The heart has four heart valves: tricuspid, pulmonary, mitral and aortic valve.

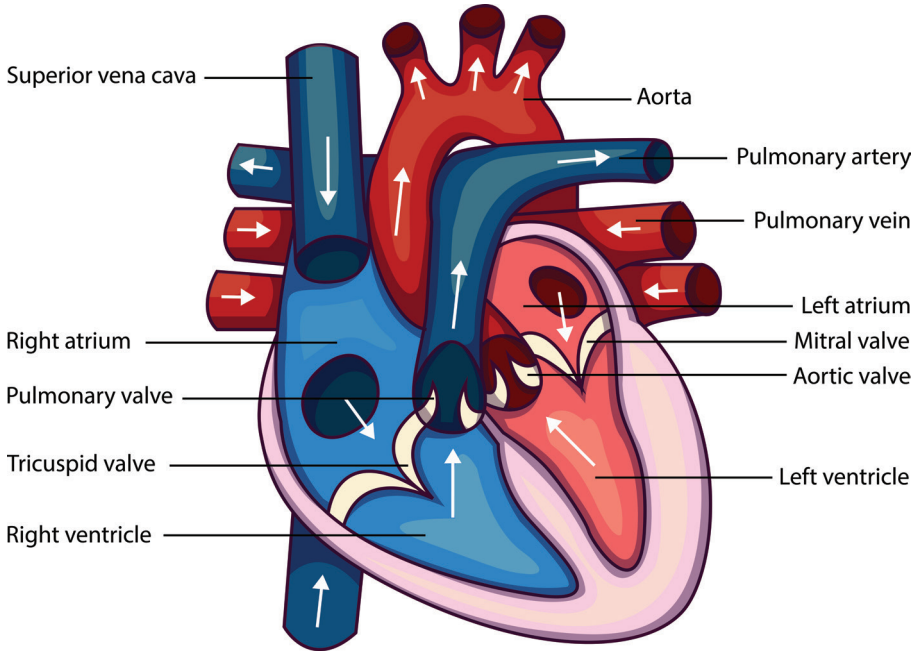


Figure 1. Anatomy of the heart

In patients with heart valve disease, the function of a heart valve is limited either due to valve stenosis or regurgitation, or a combination of both. Valve stenosis implies that the valve opening is narrowed which reduces the amount of blood that can flow through (Figure 2).[3] Valve regurgitation (also called insufficiency or leakage) implies that the valve does not close completely, allowing blood to flow backwards.[3] As a result of valve stenosis or regurgitation, the heart has to work harder to circulate the right amount of blood through the body. Consequently, patients can have symptoms of chest pain, breathlessness, fainting and fatigue. [3]

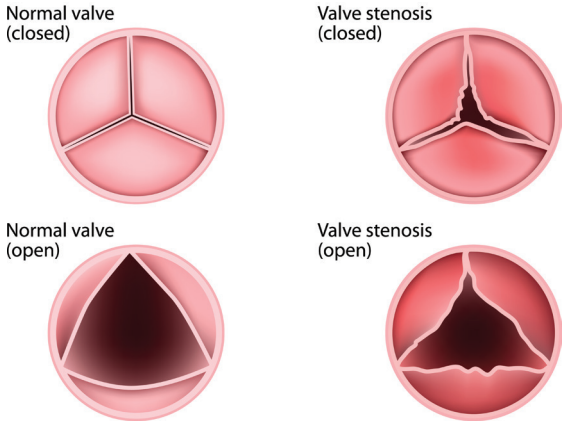


Figure 2. Heart valve stenosis

Heart valve disease represents a major global health burden. In a U.S. population-based study, the prevalence of heart valve disease in 2000 was 2.5% and increases with age.[4] According to a European wide hospital-based study, aortic stenosis is the most common heart valve disease (44.3%).[5] Heart valve disease can develop before birth (congenital) or it can be acquired later in life.[3] In the last 15 years, congenital heart disease is diagnosed in 9 per 1,000 live births worldwide, corresponding to 1.35 million new-borns with congenital heart disease every year.[6] Congenital heart valve disease often affects the aortic or pulmonary valve. Acquired heart valve disease can be caused by degeneration of heart valves, rheumatic heart disease, or infection. Degeneration of heart valves is the leading cause of heart valve disease in Europe (63%).[7] Risk factors for degeneration of heart valves are age, male sex, smoking, diabetes, and hypertension.[3] Rheumatic heart disease is the second most frequent cause of heart valve disease and was present in 22% of patients with heart valve disease in Europe. [7] Rheumatic heart disease is a consequence of rheumatic fever in which the heart valves are damaged. Rheumatic fever is caused by a streptococcal infection and can be treated with penicillin.[8] During the last decades, the health-related burden of

rheumatic heart disease has declined worldwide, but the condition persists in some of the poorest regions in the world, due to overcrowding, poor sanitation, and other social determinants of poor health.[9] Other causes of acquired heart valve disease are infective endocarditis and inflammatory heart disease.[7]

In this thesis, we focused on the heart valves in the aortic and pulmonary position. In the aortic position, we focused on elderly patients because the prevalence of aortic valve disease is the highest in these patients, due to degeneration of the native aortic valve, and therefore they represent the largest target population for TEHV.[4] In the pulmonary position, we focused on children because pulmonary valve disease is often caused by congenital heart valve disease, and the promise of 'one valve for life' with TEHV can result in the largest benefits in these young patients.[3]

CURRENT TREATMENT OF HEART VALVE DISEASE

Aortic valve

Patients who experience symptoms of severe aortic valve disease need aortic valve surgery.[3] In some patients, the diseased aortic valve can be repaired, but most commonly the diseased aortic valve needs to be replaced with a heart valve substitute using open heart surgery (i.e. surgical aortic valve replacement, SAVR) or a collapsible heart valve substitute can be placed in the aortic valve position using a catheter (transcatheter aortic valve implantation, TAVI). TAVI has emerged as an alternative to SAVR in recent years, especially in elderly patients who are inoperable or at high operable risk due to comorbidities.[10, 11] Although TAVI is a less invasive procedure than SAVR, there are also disadvantages such as the higher occurrence of paravalvular regurgitation and vascular and access site-related complications.[12] Due to its recent introduction in 2007, information on long-term outcomes after TAVI is scarce.[12] When both surgical and transcatheter aortic valve implantation are not possible, relief of symptoms can be sought with medication.

Pulmonary valve

Several complex congenital heart defects require immediate surgical anatomical correction of the right ventricular outflow tract (RVOT) with a heart valve substitute or a valved conduit from the right chamber to the pulmonary artery, for example pulmonary atresia or truncus arteriosus.[13] These patients often require re-intervention in infancy or early childhood due to pulmonary valve stenosis or regurgitation caused by somatic growth or degeneration of the valved conduit.[14] Other congenital heart defects, such as tetralogy of Fallot, can initially be corrected without implanting a heart valve substitute or valved conduit, but often these patients develop pulmonary

regurgitation and require surgical pulmonary valve replacement later in childhood or adolescence.[15] In addition, pulmonary heart valve substitutes are used during the Ross procedure in patients with aortic valve disease who not prefer or who are not eligible for other heart valve substitutes in the aortic position due to aortic regurgitation or dilatation. In this procedure, the diseased aortic valve is replaced with the patient's own pulmonary valve and a heart valve substitute is placed in the pulmonary valve position. This pulmonary heart valve substitute may need to be replaced later in life when patients outgrow the heart valve substitute or because of degeneration of the heart valve substitute.[16] Just as in aortic valve replacement, the pulmonary valve can be replaced with open heart surgery or transcatheter valve implantation. However, in young children, the pulmonary valve is mostly replaced surgically because the transcatheter valve substitutes are too large and cannot be customized to the patient like surgical heart valve substitutes.[17]

Heart valve substitutes

In surgical or transcatheter valve implantation the diseased valve is replaced with a heart valve substitute. Heart valve substitutes that are used with surgical valve replacement can be divided into biological and mechanical valves.[3] Biological valves can be divided into bioprostheses (porcine or bovine donor), allografts (human donor), and autografts (valve replacement within the same patient, i.e. pulmonary to aortic valve position).[3] For transcatheter valve implantation balloon or self-expanding bioprostheses are used. At this time it is not possible to use mechanical valves for transcatheter valve implantation. There is no perfect heart valve substitute as every heart valve substitute type has its own limitations.[18] In this thesis, we divided the long term performance of heart valve substitutes into three components:

- **Durability** is the time during which the heart valve substitute is free from valve dysfunction or deterioration expressed in valve stenosis or regurgitation. Valve dysfunction or deterioration includes the valve-related events structural valve deterioration (SVD) and non-structural valve dysfunction (NSVD). SVD refers to changes intrinsic to the valve itself, while NSVD refers to problems that do not directly involve valve components yet result in dysfunction of an operated valve.[19] The consequence of SVD and NSVD is often re-intervention.
- **Thrombogenicity** is the tendency of the heart valve substitute to produce a thrombus or clot due to contact with blood. Ideally, heart valve substitutes should be non-thrombogenic. Valve-related events related to thrombogenicity are thromboembolic events: valve thrombosis and strokes. Valve thrombosis can block a part of the blood flow path or interfere with valve function and can be treated with medication or re-intervention.[19] To prevent thromboembolic events, lifelong anticoagulation treatment is required for heart valve substitutes

with high thrombogenicity, which is associated with increased risks of bleeding and complications during pregnancy.

- **Infection resistance** is the resistance of the heart valve substitute to infections. Infection of the heart valve is called endocarditis.[19] Endocarditis can be treated with in-hospital antibiotic treatment or re-intervention.

Biological valves have the advantages that they do not require lifelong anticoagulation medication and that the ticking sound of mechanical valves is absent. However, disadvantages of biological valves are their limited durability and subsequent risk of re-intervention. Mechanical valves have the advantage that they are more durable than bioprostheses, because they are made of inorganic material, such as carbon or metal. They do, however, make a ticking sound when the valve closes and require lifelong anticoagulation due to increased thrombogenicity.[3] The treatment decision, both concerning the type of intervention and heart valve substitute is value sensitive, and should be a shared decision of the patient and a heart team (i.e. multidisciplinary group of healthcare professionals) taking into account individual patient characteristics, procedural risks, values and preferences.[18, 20]

TISSUE-ENGINEERED HEART VALVES

Tissue-engineered heart valves (TEHV) have the potential to limit or eliminate the disadvantages of existing heart valve substitutes. In contrast to biological valves, TEHV are living heart valve prostheses that are expected to have a superior durability and growth potential that would ideally make them last a lifetime. In this scenario, re-interventions because paediatric patients outgrow the heart valve substitute or re-interventions because of degeneration of the heart valve substitute would no longer be needed. Furthermore, and in contrast to mechanical valves, the risk of thromboembolic events is probably low in TEHV and therefore lifelong anticoagulation may not be required. Finally, TEHV may be more resistant to infection of the heart valve, since the heart valve substitute is made of the patient's own tissue. The above illustrates the heightened expectations of TEHV, but the development of TEHV has proved to be challenging.[2, 21]

Initially, biomedical engineers worked on creating a living heart valve outside the human body (in vitro), but the long term results were suboptimal.[2] Furthermore, it takes considerable time and costs to produce these types of TEHV and therefore they are not off-the-shelf available.[2, 22] These drawbacks of in vitro TEHV have led biomedical engineers to explore the creation of living heart valves inside the heart

of the patient (in situ) exploiting the natural regenerative potential of the human body.[2, 22] In this approach, a valve-shaped scaffold implanted in the heart of the patients recruits cells from the bloodstream and surrounding tissues and gradually transforms into a valve while the scaffold degrades.[2] Important challenges of this approach that biomedical engineers are currently facing are finding the optimal material for the scaffold that is not only biodegradable and biocompatible but also antithrombogenic and able to withstand the hemodynamic loading in the heart[22], how to induce the regeneration of functional tissue[23], finding the optimal balance between scaffold degradation and the formation of new tissue[23], and figuring out how to deal with variability in regenerative capacity between patients due to age, sex, and comorbidities (e.g. diabetes and chronic kidney failure).[23] Both surgical and transcatheter implantation of TEHV are explored.[22] Most of the currently published literature concerns the development of surgical pulmonary heart valve substitutes, however, the development of transcatheter aortic heart valve substitutes is receiving more attention because of its relevance in the large group of elderly patients with aortic valve disease.[22]

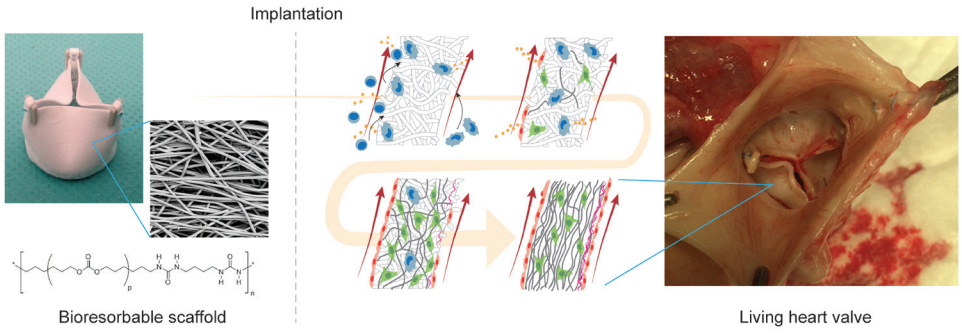


Figure 3. In-situ heart valve tissue engineering (source: Kluin et al. Biomaterials (2017) 125:101-117)

Despite the aforementioned challenges, preclinical and first-in-man clinical trials showed the promise of TEHV. The first preclinical results of in situ TEHV implanted in the pulmonary position in sheep demonstrated sustained functionality over 12 months of follow-up.[24] Further, as a first step towards the application of TEHV in humans, Xeltis BV has performed a clinical trial of tissue-engineered vascular grafts in five children (www.clinicaltrials.gov, NCT02377674). After two years, all patients were alive with adequate hemodynamic performance.[25] Finally, Xeltis BV recently initiated the first clinical feasibility trial, in which twelve children received a tissue-engineered pulmonary valved conduit (www.clinicaltrials.gov, NCT02700100). The outcomes of this trial are pending at the time of writing this thesis.

(EARLY) HEALTH TECHNOLOGY ASSESSMENT

Health Technology Assessment (HTA) is the systematic evaluation of social, economic, organizational and ethical issues of a health intervention or technology to inform policy decision making.[26] An important component of HTA is the economic evaluation in which alternative treatment options are compared in terms of their costs and consequences.[27] There are four types of economic evaluations: cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA) and cost-minimization analysis (CMA).[27] In CEAs health benefits are measured in natural units such as life years saved or improvements in functional status (e.g. New York Heart Association (NYHA) class). In CUAs health benefits are expressed in a utility based measure such as quality-adjusted life years (QALYs). In CBAs health benefits are expressed in monetary terms. In CMAs the health benefits are equivalent, therefore only the difference in costs is evaluated.[27, 28] Despite the difference in expression of health benefits, the term 'cost-effectiveness analysis' is often used for economic evaluations expressing health benefits in natural units (CEA) as well as utilities (CUA), also in this thesis. The cost-effectiveness of a new healthcare intervention is usually expressed in an incremental cost-effectiveness ratio (ICER). The ICER represents the additional costs per extra unit of effect, preferable a QALY, of the new healthcare intervention compared to the current standard treatment (Figure 4).[29]

$$\text{Incremental cost-effectiveness ratio (ICER)} = \frac{\text{Costs new treatment - Costs existing treatment}}{\text{Effects new treatment - Effects existing treatment}}$$

Figure 4. Incremental cost-effectiveness ratio

The ICER is compared to a certain cost-per-QALY threshold (Figure 5). In theory, this threshold represents the opportunity costs of healthcare spending.[30] More specifically, the comparison of the ICER with the cost-per-QALY threshold indicates whether or not the health expected to be gained from a new intervention exceeds the health expected to be lost elsewhere as other healthcare activities are displaced because the healthcare budget can only be spent once (i.e. opportunity costs).[30, 31] However, in practice, this threshold often represents the monetary value or the societal willingness to pay of a QALY.[30] In the Netherlands, the societal willingness to pay depends on disease burden with the current standard of care; the higher the disease burden, the higher the societal willingness to pay, and thus, the cost-per-QALY threshold.[32]

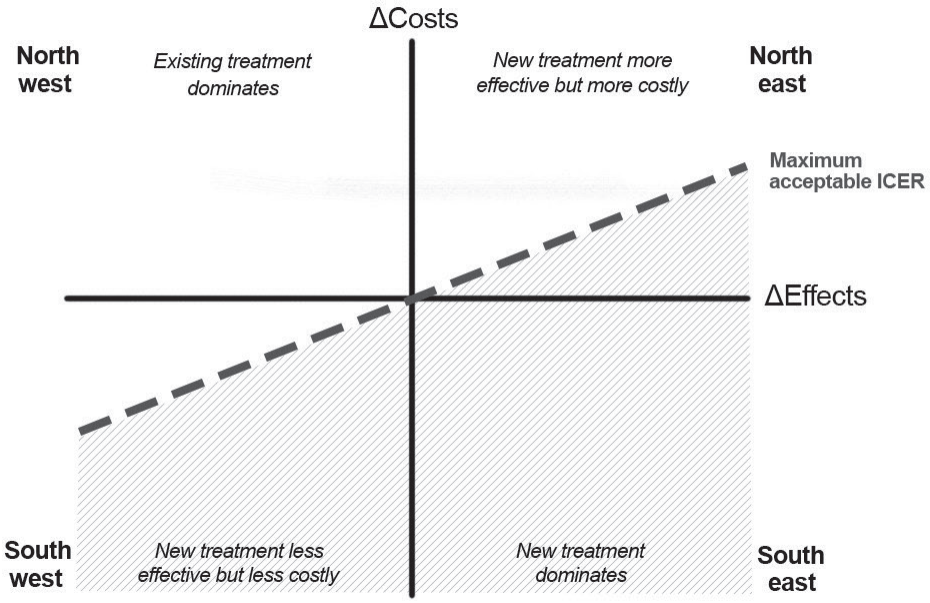


Figure 5. Cost-effectiveness plane. ICER: incremental cost-effectiveness ratio.

In light of limited resources for healthcare all over the world, there is increasing attention for cost-effectiveness of new healthcare interventions.[29] Information on cost-effectiveness can support healthcare decision makers in allocating the limited resources in a way that maximizes the health of the overall population and avoids implementation of ineffective or comparatively inefficient healthcare interventions.[33] While in cost-effectiveness analyses the focus has long been on evaluating pharmaceuticals, an increasing number of countries, such as the Netherlands and the United Kingdom, nowadays request information on cost-effectiveness in other areas, such as surgery, as well before making reimbursement decisions of new healthcare interventions.[34, 35]

HTA is often performed when the new healthcare intervention is ready for introduction in clinical practice. However, information on cost-effectiveness can also be valuable earlier in the development process. Early HTA is the use of economic evaluation in early stages of the development of new healthcare interventions mainly to guide developers at the time that investment decisions are made, for example by investigating the optimal target population.[36] It allows developers to change the direction or stop further development if the results suggest that the intervention is unlikely to be successful or become cost-effective.[36] Although early HTA is mainly performed to inform developers of new healthcare interventions, patients, clinicians and healthcare

decision makers can also benefit from timely information on the (cost-)effectiveness of potential interventions that may be used in clinical practice in the future.[37]

THESIS AIM

This thesis describes the early Health Technology Assessment of tissue-engineered heart valves. The overall aim of this thesis is to compare the health effects and costs of existing heart valve substitutes and the potential health effects and costs of tissue-engineered heart valves using a patient level simulation model. Three lines of research can be distinguished in this thesis: development of the decision-analytic model, assessment of health effects and costs of existing heart valve substitutes to estimate the input parameters of the model, and early HTA of TEHV in the aortic position in elderly patients and pulmonary position in children by applying the model.

OUTLINE

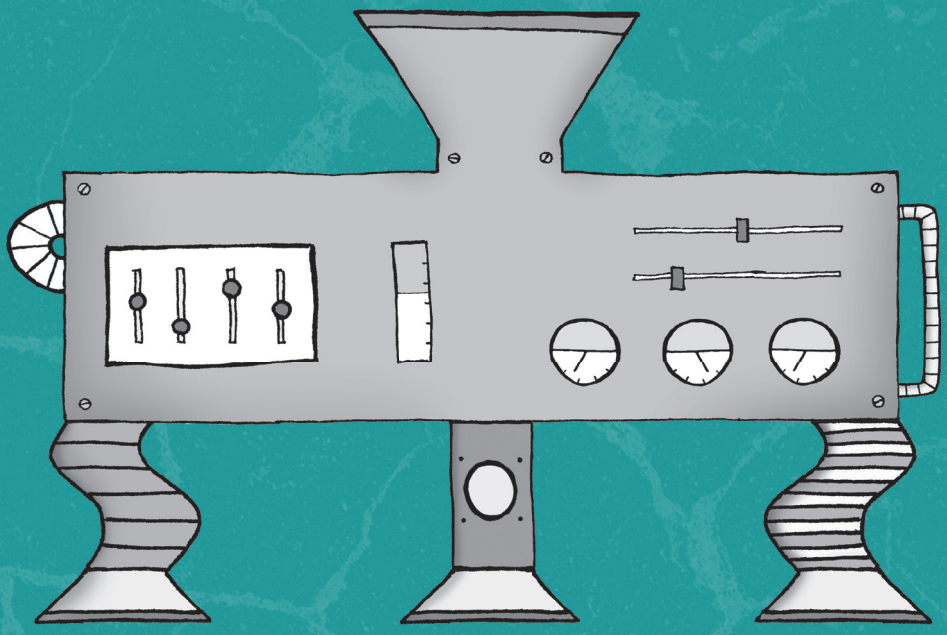
The early HTA of TEHV described in this thesis was performed by using a decision-analytic model. The appropriate development of a decision-analytic model begins with the understanding of the problem that is being addressed by constructing a conceptual model. In ***Chapter 2*** a systematic literature review describes the existing decision-analytic models for the economic evaluations of heart valve implantations and their methodological quality. ***Chapter 3*** describes how the findings of this systematic review were used in combination with input from a Delphi panel of experts, in the development of the conceptual model that served as the foundation of the decision-analytic model to estimate the cost-effectiveness of TEHV used in this thesis. Before we could perform cost-effectiveness analyses with our decision-analytic model, data needed to be collected on the input parameters of the model. Since TEHV are not implemented in clinical practice yet, assumptions had to be made about their performance and costs. In contrast to TEHV, the performance and costs of existing heart valve substitutes could be based on evidence from clinical practice. In the next chapters, the clinical outcomes, health-related quality of life, and costs of existing heart valve substitutes were assessed. In particular, ***Chapter 4*** describes a systematic review and meta-analysis of contemporary outcomes after surgical aortic valve replacement with bioprostheses and allografts in patients of all ages. To be able to use input parameters specifically for elderly patients in the early HTA of TEHV in the aortic position in elderly patients, ***Chapter 5*** presents a systematic review and meta-analysis of outcomes after surgical aortic valve replacement with bioprostheses in patients of 70 years or older. The impact of heart valve implantations goes beyond the

clinical impact on patients. Therefore, ***Chapter 6*** describes patient-reported estimates of health-related quality of life, use of informal care and productivity after heart valve implantations. In ***Chapter 7***, retrospective analysis of health insurance claims data of patients who underwent heart valve implantations provides real-world, age group-specific estimates of all healthcare costs associated with heart valve implantations, including the costs of heart valve implantations itself, complications and healthcare use in the years following the heart valve implantation. The collected data on existing heart valve substitutes was combined in early Health Technology Assessment studies to estimate the potential cost-effectiveness of tissue-engineered heart valves in elderly patients requiring aortic valve replacement in ***Chapter 8*** and in children in need of pulmonary valve replacement in ***Chapter 9***. In addition, Chapter 9 includes a systematic review and meta-analysis of contemporary outcomes after surgical pulmonary valve replacement in children. ***Chapter 10*** discusses optimal decision making in heart valve disease interventions from a clinical, patient and societal perspective. ***Chapter 11*** provides a general discussion of the three research lines of this thesis, the implications for different stakeholders, and conclusions and recommendations for further research.

REFERENCES

1. Hufnagel, C.A., et al., *Surgical correction of aortic insufficiency.* Surgery, 1954. **35**(5): p. 673-683.
2. Bouten, C.V., A. Smits, and F. Baaijens, *Can we grow valves inside the heart? Perspective on material-based in situ heart valve tissue engineering.* Frontiers in Cardiovascular Medicine, 2018. **5**: p. 54.
3. Kumar, P. and Clark, M, *Clinical medicine*. 8 ed. 2012: Elsevier.
4. Nkomo, V.T., et al., *Burden of valvular heart diseases: a population-based study.* The Lancet, 2006. **368**(9540): p. 1005-1011.
5. Iung, B., et al., *A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease.* European Heart Journal, 2003. **24**(13): p. 1231-1243.
6. van der Linde, D., et al., *Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis.* Journal of the American College of Cardiology, 2011. **58**(21): p. 2241-2247.
7. Iung, B. and A. Vahanian, *Epidemiology of acquired valvular heart disease.* Canadian Journal of Cardiology, 2014. **30**(9): p. 962-970.
8. Reményi, B., et al., *World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline.* Nature Reviews Cardiology, 2012. **9**(5): p. 297.
9. Watkins, D.A., et al., *Global, regional, and national burden of rheumatic heart disease, 1990–2015.* New England Journal of Medicine, 2017. **377**(8): p. 713-722.
10. Leon, M.B., et al., *Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery.* New England Journal of Medicine, 2010. **363**(17): p. 1597-1607.
11. Smith, C.R., et al., *Transcatheter versus surgical aortic-valve replacement in high-risk patients.* New England Journal of Medicine, 2011. **364**(23): p. 2187-2198.
12. Durko, A.P., R.L. Osnabrugge, and A.P. Kappetein, *Long-term outlook for transcatheter aortic valve replacement.* Trends in cardiovascular medicine, 2017.
13. Vitanova, K., et al., *Which type of conduit to choose for right ventricular outflow tract reconstruction in patients below 1 year of age?* Eur J Cardio-thorac Surg, 2014. **46**(6): p. 961-966.
14. Lund, A.M., et al., *Early re-intervention on the pulmonary arteries and right ventricular outflow tract after neonatal or early infant repair of truncus arteriosus using homograft conduits.* Am J Cardiol, 2011. **108**(1): p. 106-113.
15. Bell, D., et al., *Long-term performance of homografts versus stented bioprosthetic valves in the pulmonary position in patients aged 10-20 years.* European Journal of Cardio-Thoracic Surgery, 2018: p. 1-7.
16. Takkenberg, J.J.M., et al., *The Ross procedure a systematic review and meta-analysis.* Circulation, 2009. **119**(2): p. 222-228.
17. Kumar, M.T., Mark W; Rodefeld, Mark; Bell, Teresa; Brown, John W, *Right Ventricular Outflow Tract Reconstruction With a Polytetrafluoroethylene Monocusp Valve: A 20-Year Experience.* Semin Thoracic Surg, 2016. **28**: p. 463–470.
18. Baumgartner, H., et al., *2017 ESC/EACTS Guidelines for the management of valvular heart disease.* European Heart Journal, 2017. **38**(36): p. 2739-2791.
19. Akins, C.W., et al., *Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions.* European Journal of Cardio-Thoracic Surgery, 2008. **33**(4): p. 523-528.

20. Nishimura, R.A., et al., *2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines.* Circulation, 2017. **135**(25): p. e1159-e1195.
21. Yacoub, M.H. and J.J.M. Takkenberg, *Will heart valve tissue engineering change the world?* Nat Clin Pract Cardiovasc Med, 2005. **2**(2): p. 60-61.
22. Motta, S.E., et al., *Off-the-shelf tissue engineered heart valves for in situ regeneration: current state, challenges and future directions.* Expert review of medical devices, 2018. **15**(1): p. 35-45.
23. Wissing, T.B., et al., *Biomaterial-driven in situ cardiovascular tissue engineering—a multi-disciplinary perspective.* NPJ Regenerative medicine, 2017. **2**(1): p. 18.
24. Kluin, J., et al., *In situ heart valve tissue engineering using a bioresorbable elastomeric implant–From material design to 12 months follow-up in sheep.* Biomaterials, 2017. **125**: p. 101-117.
25. Bockeria, L.C., Thierry; Kim, Alex; Shatalov, Konstantin; Makarenko, Vladimir; Cox, Martijn; Svanidze, Oleg. *Polymeric bioabsorbable vascular graft in modified Fontan procedure - two-year follow-up*. in *7th World Congress of Pediatric Cardiology & Cardiac Surgery (WCPCCS)*. 2017. Barcelona.
26. World Health Organization. *Health Technology Assessment*. 2018 [cited 2018 24 August]; Available from: http://www.who.int/medical_devices/assessment/en/.
27. Drummond, M.F., et al., *Methods for the economic evaluation of health care programmes*. 2015: Oxford university press.
28. Palmer, S., S. Byford, and J. Raftery, *Economics notes: types of economic evaluation.* BMJ: British Medical Journal, 1999. **318**(7194): p. 1349.
29. Briggs, A., M. Sculpher, and K. Claxton, *Decision modelling for health economic evaluation*. 2006: OUP Oxford.
30. Brouwer, W., et al., *When is it too expensive? Cost-effectiveness thresholds and health care decision-making*. 2018, Springer.
31. Claxton, K., et al., *Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold.* Health technology assessment (Winchester, England), 2015. **19**(14): p. 1.
32. Zwaap, J.K., S; Meijden van der, C; Staal, P; Heiden van der, L, *Kosteneffectiviteit in de praktijk*, Z. Nederland, Editor. 2015.
33. Siebert, U., *When should decision-analytic modeling be used in the economic evaluation of health care?* Eur J Health Econom, 2003. **3**: p. 143.
34. Zorginstituut, N., *Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg.* Diemen: Zorginstituut Nederland, 2015.
35. Rawlins, M.D. and A.J. Culyer, *National Institute for Clinical Excellence and its value judgments.* BMJ: British Medical Journal, 2004. **329**(7459): p. 224.
36. IJzerman, M.J., et al., *Emerging use of early health technology assessment in medical product development: a scoping review of the literature.* PharmacoEconomics, 2017. **35**(7): p. 727-740.
37. Buisman, L.R., et al., *The early bird catches the worm: Early cost-effectiveness analysis of new medical tests.* International Journal of Technology Assessment in Health Care, 2016: p. 1-8.



2

Systematic review of model-based economic evaluations of heart valve implantations

Simone A. Huygens, Johanna J.M. Takkenberg, Maureen P.M.H. Rutten-van Mölken

Eur J Health Econ. 2018;19:241-255.

ABSTRACT

Objective: To review the evidence on the cost-effectiveness of heart valve implantations generated by decision-analytic models and to assess their methodological quality.

Methods: A systematic review was performed including model-based cost-effectiveness analyses of heart valve implantations. Study and model characteristics and cost-effectiveness results were extracted and the methodological quality was assessed using the Philips checklist.

Results: Fourteen decision-analytic models regarding the cost-effectiveness of heart valve implantations were identified. In most studies transcatheter aortic valve implantation (TAVI) was cost-effective compared to standard treatment (ST) in inoperable or high-risk operable patients (ICER range: €18,421-€120,779) and in all studies surgical aortic valve replacement (SAVR) was cost-effective compared to ST in operable patients (ICER range: €14,108-€40,944), but the results were not consistent on the cost-effectiveness of TAVI versus SAVR in high-risk operable patients (ICER range: dominant to dominated by SAVR). Mechanical mitral valve replacement (MVR) had the lowest costs per success compared to mitral valve repair and biological MVR. The methodological quality of the studies was moderate to good.

Conclusion: This review showed that improvements can be made in the description and justification of methods and data sources, sensitivity analysis on extrapolation of results, subgroup analyses, consideration of methodological and structural uncertainty, and consistency (i.e. validity) of the models. There are several opportunities for future decision-analytic models of the cost-effectiveness of heart valve implantations: considering heart valve implantations in other valve positions besides the aortic valve, using a societal perspective, and developing patient-simulation models to investigate the impact of patient characteristics on outcomes.

INTRODUCTION

The first cost-effectiveness analysis on heart valve implantations was published by Wu et al. in 2007.[1] They estimated the cost-effectiveness of surgical aortic valve replacement (SAVR: native heart valve is replaced with a prosthetic heart valve during open heart surgery) compared to standard treatment (ST: often medical management) and found that SAVR was cost-effective.[1] The number of cost-effectiveness analyses on heart valve implantations increased after the introduction of an alternative treatment for severe aortic valve stenosis: transcatheter aortic valve implantation (TAVI: prosthetic heart valve is implanted with a catheter, no open heart surgery required).

In 2010, the first model-based cost-effectiveness analysis of TAVI compared to ST and SAVR concluded that TAVI had high potential to be cost-effective for inoperable patients, but the cost-effectiveness of patients with lower operable risk was uncertain. [2] Healthcare decision makers required further evidence on the clinical effectiveness of TAVI to make a reimbursement decision. The Placement of Aortic Transcatheter Valves (PARTNER) trial was the first randomized controlled trial for TAVI.[3, 4] Based on the PARTNER trial results, in 2012 the National Institute for Health and Care Excellence approved reimbursement of TAVI for inoperable patients in the UK but reimbursement for operable patients is still under review.[5]

Since then almost every cost-effectiveness analysis investigating TAVI based their clinical effectiveness parameters on the PARTNER trial. There are two trial-based cost-effectiveness analyses[6, 7]; the other cost-effectiveness analyses are based on decision-analytic models. Decision-analytic models represent an explicit way to synthesize evidence on the outcomes and costs of alternative interventions.[8]

We are currently developing a decision-analytic model to estimate the cost-effectiveness of current and future heart valve interventions (e.g. tissue-engineered heart valves). [9] In this light, careful review of existing decision-analytic models addressing related problems is a prerequisite.[10]

The goal of this study is to investigate the opportunities for new decision-analytic models in the field of heart valve interventions and to learn from the methodological choices made by previous model developers. Therefore, and in contrast with previous reviews [11-13], we focus on decision-analytic models and exclude cost-effectiveness analyses alongside clinical trials. Furthermore, we are not only interested in decision-analytic models investigating the cost-effectiveness of SAVR and TAVI but we also include decision-analytic models for other heart valve implantations.

METHODS

Search strategy and selection criteria

This systematic review was conducted according to PRISMA guidelines.[14] On May 28, 2015 several databases were searched (Supplementary Material). Two reviewers (SH & JT or SH & MR) independently determined whether the publications met the inclusion criteria. In case of disagreement, an agreement was negotiated. Publications were included when they reported model-based economic evaluations considering costs and health outcomes of heart valve implantations. Papers solely describing regression models, cost-analyses, non-English publications, conference abstracts, editorials and letters to the editor were excluded. References of selected papers and previous systematic reviews [11-13] were crosschecked for other relevant studies.

Data extraction

Study and model characteristics and cost-effectiveness results were extracted (Supplementary Material). Costs were inflated to 2015 and converted to euros (€) using purchaser power parities and exchange rates.[15, 16]

Cost-effectiveness thresholds

Reported cost per quality adjusted life years (QALY) ratios were compared to thresholds used in individual studies and thresholds based on the WHO-CHOICE approach where interventions are highly cost-effective when they have an incremental cost-effectiveness ratios (ICER) below the gross domestic product (GDP)/capita, cost-effective if the ICER is 1-3 times the GDP/capita, and not cost-effective when the ICER is more than 3 times the GDP/capita.[17, 18]

Methodological quality assessment

The 'Drummond checklist' [19] and 'Evers checklist' [20] are often used to appraise methodological quality of economic evaluations conducted alongside clinical trials. Although these checklist are relevant, they are not sufficient to appraise the quality of model based economic evaluations. Therefore, we chose to use the Philips checklist to critically appraise the methodological quality of studies.[8] This checklist is divided in three sections: structure, data and consistency. Within each section criteria can be fulfilled, not fulfilled or not applicable. The checklist was assessed for every study by two reviewers (SH & JT or SH & MR). In case of disagreement, an agreement was negotiated. This assessment had a qualitative nature and studies were not excluded because of low quality scores.

RESULTS

The literature search resulted in 1,019 studies, of which 14 studies were included (Figure 1).[2, 21-33]

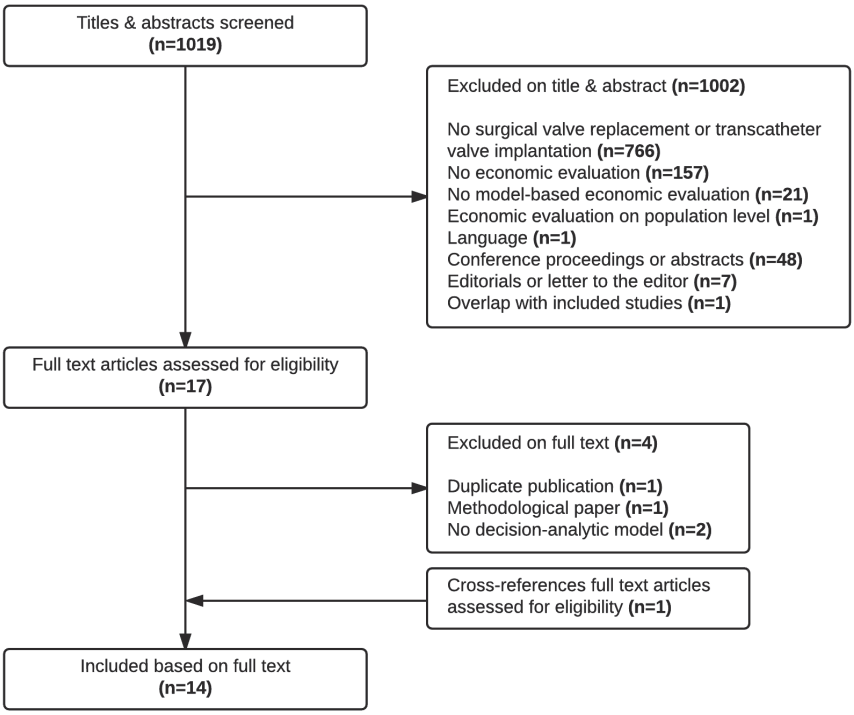


Figure 1. Study selection. TVI: transcatheter valve implantation. SVR: surgical valve replacement.

Study and model characteristics

Table 1 and 2 provide an overview of study and model characteristics. Table 1 is structured by valve position and interventions and comparators; TAVI versus ST (often inoperable patients), TAVI versus SAVR (often high operable risk patients), SAVR versus ST (operable patients) and mitral valve repair versus mitral valve replacement (operable patients).

Cost-effectiveness outcomes

Table 3 shows the cost-effectiveness outcomes structured by valve position and interventions and comparators. The cost-effectiveness thresholds used in individual studies can be found in Table 2.

TAVI versus ST (often inoperable patients)

The costs of TAVI compared to ST were higher but QALYs gained were also higher. According to thresholds used in individual studies, TAVI is cost-effective compared to ST in eight studies [2, 22, 25-27, 30, 31, 33] and not cost-effective in four studies.[23, 28, 29, 32] When applying the WHO-CHOICE approach, TAVI is cost-effective compared to ST in all studies and even highly cost-effective (ICER < GDP/capita) in seven studies.[2, 22, 25-27, 30, 33]

TAVI versus SAVR (often high-risk operable patients)

TAVI was dominated by SAVR (i.e. higher costs, lower QALY gain) in three studies [23, 26, 30], high ICERs were reported in three studies [2, 25, 29], and TAVI was dominant in one study [24] (i.e. lower costs, higher QALY gain). According to thresholds used in individual studies, TAVI was not cost-effective in two of three studies where TAVI was not dominant or dominated by SAVR.[2, 29] Using the WHO-CHOICE approach, TAVI was not cost-effective compared to SAVR in Neyt et al. [29], and TAVI was cost-effective in the SHTG report [2] and in Gada et al.[25]

SAVR versus ST (operable patients)

SAVR gains more QALYs at higher costs than ST. According to thresholds used in individual studies and the WHO-CHOICE approach SAVR is (highly) cost-effective compared to ST in all studies.

Mitral valve repair versus mitral valve replacement (operable patients)

One study evaluated heart valve implantations in the mitral valve position.[21] They found that mechanical mitral valve replacement has the lowest costs per success (when using a 20-year time horizon). To compare these results with heart valve implantations in other valve positions and to assess whether it falls below the cost-effectiveness threshold, the effects should be expressed in QALYs.

Methodological quality assessment

The assessment of methodological quality of studies using the Philips checklist is reported in Table S1 in the Supplementary Material. The total score represents the percentage of criteria that were fulfilled, corrected for criteria that were not applicable, and ranged from 49-87%. The lowest percentage was found in the study on mitral valve interventions.[21]

Table 1. Study characteristics

Author and year of publication	Target population	Clinical effectiveness data source*	Mean patient age, years		Logistic EuroSCORE		NYHA class III/IV, %		Intervention of interest	Comparator
			I	C	I	C	I	C		
TAVI versus ST (often inoperable patients)										
SHTG 2010 [2]	***Medium risk AS patients:*** Patients for whom there is currently not a clear choice of treatment, as such the choice considered in the analysis is between SAVR, TAVI and MM.	Revive	70	70	NR	NR	NR	NR	TAVI (unclear if TF and/or TA)	MM
	High-risk AS patients: Patients who are ineligible for conventional surgery so traditionally get medical management, as such the choice is between TAVI and MM.		80	80						
Gada 2012 [25]	***High-risk severe AS operable patients:*** Patients with a logistic EuroSCORE>15% and/or STS score>10%.	8 registries	82	77	26	21	87	90	TAVI (TF)	MM[1]
Gada 2012 [26]		20 registries	82	81	29	31	77	87	TAVI (TA)	
Neyt 2012 [29] Watt 2012 [33] Doble 2013 [23] Hancock-Howard 2013 [27] Murphy 2013 [28] Queiroga 2013 [31] Simons 2013 [32]	***Inoperable SSAS patients:*** Patients with coexisting conditions associated with a predicted probability of ≥50% of death by 30 days after surgery or a serious irreversible condition. At least two surgeon investigators had to agree that the patient was not a suitable candidate for surgery.	PARTNER-B	83	83	26	30	92	94	TAVI (TF)	ST (including MM and/or BAV)
Orlando 2013 [30]	***Patients unsuitable for SAVR:*** Patients with coexisting conditions associated with a predicted probability of ≥50% of death by 30 days after surgery or a serious irreversible condition. At least two surgeon investigators had to agree that the patient was not a suitable candidate for surgery.	PARTNER-B	83	83	26	30	92	94	TAVI[2]	MM

Table 1. Continued

Author and year of publication	Target population	Clinical effectiveness data source*	Mean patient age, years		Logistic EuroSCORE		NYHA class III/IV, %		Intervention of interest	Comparator
			I	C	I	C	I	C		
Brecker 2014 [22]	***Inoperable and high-risk SSAS patients:*** Patients considered inoperable or at higher risk for SAVR and anatomically acceptable candidates for elective treatment with the CoreValve System.	ADVANCE (all TAVI patients) PARTNER-B (ST patients)	81	83	19	30	80	94	TAVI (TF, direct aortic, or subclavian)	ST (including MM and/or BAV)
		ADVANCE (TAVI patients with >20% logistic EuroSCORE) PARTNER-B (ST patients)	83	83	32	30	85	94		
TAVI versus SAVR (often high-risk operable patients)										
SHTG 2010 [2]	***Low-risk AS patients:*** Patients who are assumed to be eligible for SAVR but for whom TAVI could be an alternative.	Revive	60	60	NR	NR	NR	NR	TAVI (unclear if TF and/or TA)	SAVR
	Medium risk AS patients: Patients for whom there is not currently a clear choice of treatment, as such the choice considered in the analysis is between SAVR, TAVI and MM.		70	70						
Gada 2012 [25]	***High-risk severe AS operable patients:*** Patients with a logistic EuroSCORE>15% and/or STS score>10%.	8 registries	82	77	26	21	86	90	TAVI (TF)	SAVR
Gada 2012 [26]		20 registries	82	81	29	31	77	87	TAVI (TA)	
Neyt 2012 [29] Doble 2013 [23] Fairbairn 2013 [24]	***High-risk operable SSAS patients:*** Patients with a predicted risk of operative mortality rate of ≥15% or a Society of Thoracic Surgery risk score of ≥10%.	PARTNER-A	84	85	29	29	94	94	TAVI (TF+TA)	SAVR
Orlando 2013 [30]	***Patients suitable for SAVR:*** TAVI and MM patients Inoperable SSAS patients from the PARTNER-B trial: Patients with coexisting conditions associated with a predicted probability of ≥50% of death by 30 days after surgery or a serious irreversible condition. At least two surgeon investigators had to agree that the patient was not a suitable candidate for surgery. SAVR patients Patients undergoing isolated SAVR.	PARTNER-B (for TAVI and MM) and two cohort studies [50, 51] (SAVR)	83	NR	29	10-20	92	NR	TAVI (TF+TA)	SAVR (90%) MM (10%)

Table 1. Continued

Author and year of publication	Target population	Clinical effectiveness data source*	Mean patient age, years		Logistic EuroSCORE		NYHA class III/IV, %		Intervention of interest	Comparator
			I	C	I	C	I	C		
SAVR versus ST (operable patients)										
SHTG 2010 [2]	***Medium risk AS patients:*** Patients for whom there is not currently a clear choice of treatment, as such the choice considered in the analysis is between SAVR, TAVI and MM.	Revive	70	70	NR	NR	NR	NR	SAVR	MM
Gada 2012 [25]	***High-risk severe AS operable patients:*** Patients with a logistic EuroSCORE>15% and/or STS score>10%.	8 registries	82	77	26	21	86	90	SAVR	MM[1]
Gada 2012 [26]		20 registries	82	81	29	31	77	87		
Mitral valve repair versus replacement (operable patients)										
Beresniak 2013 [21]	Patients with mitral valve disease undergoing surgical mitral valve repair or replacement	Cohort study of the Georges Pompidou European Hospital	NR	NR	NR	NR	NR	NR	Surgical mitral valve repair	Surgical mitral valve replacement

*The sources of other data types (mortality, resource sue, costs and utilities) can be found in Table S2.
I: intervention of interest. C: comparator. NR: not reported. SSAS: severe symptomatic aortic stenosis; defined as an aortic valve area 0.8 cm2 with either a mean valve gradient >40 mm Hg or a peak jet velocity >4.0 m/s. AS: aortic stenosis. SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve replacement. TF: transfemoral. TA: transapical. MM: medical management. ST: standard therapy; including MM and/or balloon aortic valvuloplasty (BAV). NYHA class: New York Heart Association class. PARTNER-A: comparing TAVI with SAVR in high-risk operable patients.[3] PARTNER-B: comparing TAVI with MM/ST in inoperable patients.[4] REVIVE: The Registry of Endovascular Implantation of Valves in Europe trial started in 2003 in a single centre in France with the aim to study the feasibility and safety of TAVI in inoperable patients.[52] ADVANCE: Multicentre, non-randomized study that included 44 centres in 12 countries evaluating the outcomes of a self-expanding transcatheter aortic valve system in patients considered inoperable or at a higher surgical risk.[53]

Table 2. Model characteristics

Author and year of publication	Model type	Health states	Time horizon	Cycle length	Discount rate	Study perspective	Country
SHTG 2010 [2]	Decision tree Markov model	Short-term: dead, alive, major (assumed to result in failure of the valve implantation with the patient left in a state no better than their original manifestation of AS), minor (assumed to resolve with appropriate medical care), or no procedure related event, convert to SAVR, convert to MM, AS/ failed valve replacement, and functioning valve replacement. Long-term: AS/failed valve replacement, procedure related event, functioning valve replacement, death.	1 month; until the majority of patients have died	NA; 1 year	C: 3.5% E: 3.5%	Healthcare	UK
Gada 2012 [25] Gada 2012 [26]	Markov model	Medical management, screened for TAVI, SAVR and peri-procedural risks, TAVI and peri-procedural risks, post-SAVR or TAVI complication (including endocarditis, hemorrhage, valve thrombosis, and non-cerebral), heart failure, stroke, dead.	Lifetime	1 year	C: 5% E: -	Healthcare payer	US
Neyt 2012 [29]	Markov model	Mortality, hospitalization, other events (repeat hospitalization, minor/major stroke and TIA, and cardiac re-interventions), and no event.	Lifetime/ 1 year[1]	1 month	C: 3% E: 1.5%	Healthcare	Belgium
Watt 2012 [33]	Two interlinked Markov models	Short-term: ICU non-ICU, home care, post-hospital rehabilitation (community and managed) and death. Long-term: home care, reoperation and death.	1 month; 10 years	1 day; 1 month	C: 3.5% E: 3.5%	Healthcare	UK
Beresniak 2013 [21]	Decision tree	Sequential treatment switches allowed at each 5-year interval in case of failure of the former treatment option.	10/20 years	NA	C: - E: -	Healthcare	France
Doble 2013 [23]	Decision tree Markov model	Short-term: alive without complications, other acute complications (endocarditis, major vascular complications, paravalvular leaks, PI, major bleeding, AF), stroke (temporary or permanent disability), MI, AKI (no, temporary, and permanent dialysis), reoperation, conversion to SAVR, cumulative death. Long-term: alive without complications, stroke first year, stroke subsequent years, MI first year, MI subsequent years, post-AKI, alive and death after complications, and death.	1 month; 20 years	NA; 1 year	C: 5% E: -	Healthcare	Canada
Fairbairn 2013 [24]	Decision tree Markov model	Short-term: after TAVI/SAVR transition to NYHA class I-IV or dead. Long-term: transitions from NYHA class I-IV to dead.	2 years; 10 years	NA; 1 year	C: 3.5% E: 3.5%	Healthcare	UK

Table 2. Continued

Author and year of publication	Model type	Health states	Time horizon	Cycle length	Discount rate	Study perspective	Country
Hancock-Howard 2013 [27]	Decision tree	After treatment: alive or dead. When alive: early or no early complication. After both these health states: late complication (major stroke with full recovery, major stroke with ongoing care and no stroke) or no late complication. Complications in no stroke: valve thromboembolism, PI, endocarditis, reoperation, MI, renal failure, BAV, hospital readmission, SAVR. In addition to these complications, other complications were only considered early: major access site/vascular complication, major paravalvular leak, and arrhythmia/atrium fibrillation.	3 years	NA	C: 5% E: 5%	Healthcare	Canada
Murphy 2013 [28][2]	Decision tree Markov model	Short-term: dead, alive, major (e.g. valve thromboembolism or MI: long-term effect), minor (e.g. PI or vascular events: short-term effect), or no procedure related event, convert to SAVR, convert to MM, AS/failed valve replacement, and functioning valve replacement. Long-term: AS/failed valve replacement, procedure related event, functioning valve replacement, and death.	1 month; Lifetime	NA; 1 year	C: - E: -	Healthcare	UK
Orlando 2013 [30]	Decision tree	Suitable for surgery followed by SAVR, TAVI (when available) and MM. Not suitable for surgery followed by TAVI (when available) and MM. After treatment: hospital-free survival and other survival (surviving patients who had undergone ≥1 episode of hospitalization after initial treatment).	1 month; 25 years	NA	C: 3.5% E: 3.5%	Healthcare	UK
Queiroga 2013 [31]	Markov model	Survival and death.	5 years	3 months	C: 5% E: 5%	Healthcare	Brazil
Simons 2013 [32]	Markov model	Health states based on combination symptom status (NYHA class I/II or III/IV) and major complications (stroke, vascular complication, bleed).	Lifetime	1 month	C: 3% E: 3%	Healthcare[3]	US
Brecker 2014 [22][4]	Two interlinked Markov models	Short-term: ICU, non-ICU, home care, post-hospital rehabilitation (community and managed) and death. Long-term: home care, reoperation and death.	1 month; 5 years	1 day; 1 month	C: 3.5% E: 3.5%	Healthcare	UK

C: costs. E: effects. NA: not applicable. AS: aortic stenosis. SAVR: surgical aortic valve replacement. TAVI: transcatheter valve implantation. BAV: balloon aortic valvuloplasty. MM: medical management. ICU: intensive care unit. PI: pacemaker implantation. AF: atrial fibrillation. MI: myocardial infarction. AKI: acute kidney injury. TIA: transient ischemic attack. NYHA: New York Heart Association. Healthcare perspective: includes all direct healthcare costs regardless of who pays them. Healthcare payer perspective: includes all direct healthcare costs covered by the health insurer (i.e. the amount of costs reimbursed to the provider).

[1]The time horizon is lifetime in the model comparing TAVI with ST in inoperable patients and 1 year in the model comparing TAVI versus SAVR in high-risk operable patients.

[2]Based on model of SHTG 2010.[2]

[3]Societal perspective according to authors, but costs outside of healthcare are not taken into account.

[4]Same model as Watt et al. 2012.[33]

Table 3. Cost-effectiveness outcomes

Author and year of publication	Subgroups	Health outcomes				Costs in 2015€ (PPPs)			Cost-effectiveness		WTP threshold	
TAVI versus ST (often inoperable patients)												
			TAVI (absolute)	ST (absolute)	TAVI vs. ST (incremental)	TAVI (absolute)	ST (absolute)	TAVI vs. ST (incremental)	ICER as reported	ICER in 2015€ (PPPs)	Individual studies	WHO approach in 2015€ (PPPs)*
SHTG 2010 [2]	medium-risk	QALY	2.9	1.53	1.37	46,690	20,253	26,436	NR	NR	£30,000	125,199
	high-risk	QALY	2.18	1.53	0.65	41,548	20,258	21,290	£ 22,603	32,774		
Gada 2012 [25]		QALY	1.78	NR	NR	58,193	NR	NR	US$ 39,964	39,084	US$ 100,000	168,198
Gada 2012 [26]		QALY	1.66	NR	NR	54,477	NR	NR	US$ 44,384	42,622	US$ 100,000	168,198
Neyt 2012 [29]		QALY	NR	NR	0.74	NR	NR	38,751	€ 44,900	52,407	Based on UK: €22,800-34,200	137,727
		LY	NR	NR	0.88	NR	NR	38,751	€ 42,600	49,722		
Watt 2012 [33]		QALY	2.36	0.80	1.56	43,125	7,140	35,985	£16,200	23,133	£20,000	125,199
Doble 2013 [23]		QALY	NR	NR	0.60	70,227	45,742	24,486	CDN$ 51,324	40,502	CDN$ 50,000	132,891
		LY	NR	NR	0.85	70,227	45,742	24,486	CDN$ 36,458	28,771		
Hancock-Howard 2013 [27]		QALY	1.33	0.84	0.49	47,376	34,641	12,735	CDN$ 32,170	26,117	CDN$ 20,000-100,000	132,891
Murphy 2013 [28]		QALY	1.63	1.19	0.44	38,685	16,786	21,899	£35,956	49,569	£20,000-30,000	125,199
		LY	2.54	2.24	0.30	38,685	16,786	21,899	NR	NR		
Orlando 2013 [30]		QALY	2.85	0.98	1.87	39,745	5,265	34,480	£12,900	18,421	£20,000-30,000	125,199
Queiroga 2013 [31]		LY	2.5	1.53	0.97	71,245	20,742	50,503	R$ 90,161	52,215	based on US: R$ 100,000	NA
Simons 2013 [32]	without BAV	QALY	1.93	1.19	0.73	168,791	83,447	85,444	US$ 116,500	116,287	$100,000	168,198
		LY	2.93	2.08	0.86	168,791	83,447	85,444	US$ 99,900	99,718		

Table 3. Continued

Author and year of publication	Subgroups	Health outcomes				Costs in 2015€ (PPPs)			Cost-effectiveness		WTP threshold	
	with ≥1 BAV	QALY	1.93	1.24	0.69	168,791	86,142	82,649	US$ 121,000	120,779		
		LY	2.93	1.97	0.96	168,791	86,142	82,649	US$ 85,700	85,544		
Brecker 2014 [22]	All patients	QALY	2.29	0.78	1.51	46,256	17,795	28,461	£13,943	18,863	£20,000	125,199
	Patients with >20% logistic EuroSCORE	QALY	2.02	0.78	1.24	47,524	17,749	29, 775	£17,718	23,970		
TAVI versus SAVR (often high-risk operable patients)												
SHTG 2010 [2]	low-risk	QALY	3.71	3.65	0.06	51,942	45,004	6,939	£87,293	124,652	£30,000	125,199
	medium-risk	QALY	2.90	2.82	0.08	45,981	38,167	7,814	£72,412	103,402		
Gada 2012 [25]		QALY	1.78	1.72	0.06	58,193	55,099	3,094	US$ 52,773	51,611	US$ 100,000	168,198
Gada 2012 [26]		QALY	1.66	1.70	-0.04	54,477	54,381	96	dominated	dominated	US$ 100,000	168,198
Neyt 2012 [29]		QALY	NR	NR	0.03	NR	NR	23,807	around €750,000	above €750,000	Based on UK: €22,800-34,200	137,727
Doble 2013 [23]		QALY	NR	NR	-0.10	67,674	58,872	8,801	dominated	dominated	CDN$ 50,000	132,891
		LY	NR	NR	0.01	67,674	58,872	8,801				
Fairbairn 2013 [24]		QALY	2.81	2.75	0.06	72,505	74,366	-1,862	dominant	dominant	£20,000	125,199
Orlando 2013 [30]		QALY	2.85	3.46	-0.61	39,745	28,375	11,370	dominated	dominated	£20,000-30,000	125,199

Table 3. Continued

Author and year of publication	Subgroups	Health outcomes				Costs in 2015€ (PPPs)			Cost-effectiveness		WTP threshold	
SAVR versus ST (operable patients)												
			SAVR (absolute)	ST (absolute)	SAVR vs. ST (incremental)	SAVR (absolute)	ST (absolute)	SAVR vs. ST (incremental)	ICER as reported	ICER in 2015€ (PPPs)	Individual studies	WHO approach in 2015€ (PPPs)*
SHTG 2010 [2]	medium-risk	QALY	2.82	1.53	1.29	38,167	19,946	18,221	£9,880	14,108	£30,000	125,199
Gada 2012 [25]		QALY	1.72	NR	NR	55,099	NR	NR	US$ 39,280	38,415	US$ 100,000	168,198
Gada 2012 [26]		QALY	1.70	NR	NR	54,381	NR	NR	US$ 42,637	40,944	US$ 100,000	168,198
Mitral valve repair versus mitral valve replacement (operable patients)												
			Health outcomes			Costs in 2015€ (PPPs)			Costs/success			
			Repair	Replacement		Repair	Replacement		Repair	Replacement		
			(absolute)	biological (absolute)	mechanical (absolute)	(absolute)	biological (absolute)	mechanical (absolute)		biological	mechanical	
Beresniak 2013 [21]	10 year time horizon	succes rate	88.3	71.7	70.4	31,414	35,501	38,499	41,773	58,138	64,212	
	20 year time horizon	succes rate	33.4	30.2	51.6	33,457	44,632	48,956	117,619	173,531	111,402	

NR: not reported. NA: not available. SAVR: surgical aortic valve replacement. TAVI: transcatheter valve implantation. BAV: balloon aortic valvuloplasty. MM: medical management. ST: standard therapy; including MM and/or BAV. ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life years. LY: life years. WTP: willingness-to-pay. *three times GDP/capita of country of interest.

DISCUSSION

Cost-effectiveness outcomes

Even though most studies compared the same heart valve implantations, cost-effectiveness results varied substantially between studies. Based on thresholds from individual studies or using the WHO-CHOICE approach, TAVI was cost-effective compared to ST in inoperable or high-risk operable patients in most studies and in all studies SAVR was cost-effective compared to ST in operable patients. The results were not consistent on the cost-effectiveness of TAVI versus SAVR in high-risk operable patients, ranging from TAVI being dominant to being dominated by SAVR. However, the cost-effectiveness thresholds were relatively high. The thresholds used in individual studies ranged from £20,000/QALY to CDN$100,000/QALY and thresholds based on the WHO-CHOICE approach ranged from €123,264/QALY for France to €168,198/QALY for the US. When we apply the threshold of the UK (£30,000 ≈ $43,000/QALY), TAVI is cost-effective compared to ST in seven instead of eight (according to thresholds used in individual studies) or all (according to WHO-CHOICE approach) studies. Just as with the individual studies' and WHO approach threshold, SAVR is cost-effective compared to ST in all three studies. Using the UK threshold does not influence our conclusion on the cost-effectiveness of TAVI versus SAVR; it remains not cost-effective in all but one study. Our results did not reflect a clear trend in the cost-effectiveness of heart valve implantations over time; probably due to the short time frame in which the studies were performed (>80% in 2012-2013).

Methodological quality assessment

There was no correlation between methodological quality scores and ICERs of the included studies (Spearman's rank correlation coefficients: TAVI vs. ST (12 studies) = 0.000, TAVI vs. SAVR (7 studies) = -0.126, SAVR vs. ST: correlation not determined because there were only three studies in this subgroup). The methodological quality assessment showed that the decision-analytic models were of moderate to good quality. However, authors did not always justify their choices and assumptions and major improvements can be made in the description of methodology. The following discusses our assessment of the methodological quality, structured according to the Philips checklist.[8]

Perspective

Most studies used a healthcare perspective (i.e. include all direct healthcare costs) and two studies used a healthcare payer perspective (i.e. only includes healthcare costs covered by the health insurer or the NHS)[25, 26]. Simons et al. [32] claimed to use a societal perspective while only healthcare costs were included. Contrary to our expectations, studies performed from a healthcare payer perspective did not report

significantly lower costs. However, it is possible that the studies performed from a healthcare payer perspective underestimated the costs of TAVI because they both assume that payers would provide the same reimbursement for the TAVI and SAVR procedure and subsequent hospitalisation.[25, 26]

The ICERs are generally the lowest in the UK and the highest in the US. Comparisons of studies within the US, showed that the costs of TAVI in Gada et al. [25, 26] are considerably lower than in Simons et al. [32], probably due to the healthcare payer perspective of Gada et al. compared to the healthcare perspective of Simons et al., the assumption of same procedure costs for TAVI and SAVR in Gada et al. while TAVI is, in general, more expensive, and/or difference in operable risks (high-risk operable patients in Gada et al. and vs. inoperable patients in Simons et al.).

Rationale for structure

Many studies combined a short- (often 1 month) and long-term model, mostly decision trees and Markov models. Health states were based on treatment [21], ward or site where care was provided [22, 33], New York Heart Association (NYHA) class [24], complications [2, 23, 25-29], survival [31], combination of NYHA class and treatment or complications.[30, 32] In our view, two studies chose a too simplistic model structure only including health states of survival and death [31] or NYHA classes and death [24] without explicitly including valve-related complications. The simple model structure did not result in divergent results compared to other studies in Queiroga et al. [31], but Fairbairn et al. [24] found that TAVI is dominant while all other studies comparing TAVI with SAVR found high ICERs or that TAVI was dominated by SAVR.

Only one study described who was involved in developing the model structure.[33] Two studies reported information about developing the model structure [22, 32], but they did not explicitly discuss this process nor referred to an underlying conceptual model. Cooper et al. also found that few studies (10%) report the development process of the model structure.[34] Transparency of model development is important to assess to what extend model development is based on clinical considerations and/or considerations regarding data availability of model parameters.[10]

Structural assumptions

Several structural assumptions were not reasonable and some might have impacted the cost-effectiveness results. For instance, four studies assumed that valve prosthesis functionality and/or complication rates were similar for TAVI and SAVR [25, 26, 33] or assumed TAVI valves retain functionality during the patient's lifetime.[24] These assumptions might over- or underestimate the effects of TAVI, because several studies

found significant differences in post-procedure complications between TAVI and SAVR [3, 35] and since TAVI is a relatively new procedure the long-term effects are unclear.

Further, Orlando et al. [30] assumed that TAVI and ST patients in the state 'survival with ≥ 1 episode of hospitalisation after initial treatment' have the same costs and QALY outcomes, regardless of how many further hospital admissions occur. If the frequency of further admissions and reasons for admissions (and thus costs and quality of life) are different between TAVI and ST patients, this assumption leads to bias in cost-effectiveness outcomes which might explain the relative low ICER reported in this study.[30]

Strategies and comparators

Many studies evaluated TAVI, but the implantation routes differed. Most studies investigated transfemoral TAVI (through the leg), while others investigated transapical TAVI (through the chest cavity), or combinations of implantation routes. Further, almost all studies investigated balloon-expendable transcatheter valve prostheses, while one study [22] evaluated self-expanding transcatheter valve prostheses. There was no clear trend in cost-effectiveness outcomes of studies considering different implantation routes or types of prostheses. However, two studies using comparable methods to determine the cost-effectiveness of both implantation routes reported a more favourable ICER for transfemoral than transapical TAVI compared to ST and SAVR. [25, 26] This might be explained by higher disease severity of patients undergoing transapical TAVI; which are often patients with a porcelain aorta who are not eligible for transfemoral TAVI.

The definition of 'standard treatment (ST)' or 'medical management (MM)' differed between studies. In studies based on the PARTNER trial [22, 23, 27-29, 31-33] ST includes MM and is combined with balloon aortic valvuloplasty (BAV) in more than 80% of patients. In other studies the comparator is MM without BAV. The ICERs of studies considering sole MM are not clearly different from studies considering ST as comparator. However, Simons et al. [32] performed separate analyses for TAVI compared to ST with and without BAV and found a more favourable ICER for TAVI compared to ST without BAV than with BAV.[32]

Time horizon

The appropriate time horizon when evaluating the cost-effectiveness of heart valve implantations is lifetime, because the interventions affect mortality rates.[36] Although the time horizons of the studies might seem different, time horizons of 10 years or longer are equivalent to lifetime because of the high age of patients undergoing valve replacement (±80 years). In four studies the time horizon is too short (1-5 years) to

capture all relevant differences between interventions.[22, 27, 29, 31] There was no clear association between time horizon and cost-effectiveness outcomes. Except for the study of Neyt et al. who reported a high ICER of TAVI compared to SAVR, that might be explained by the short time horizon (1 year) during which the high procedure costs cannot be compensated with potential increased life expectancy.[29]

Cycle length
Common practice after heart valve implantations is to schedule follow-up visits at least once a year.[37] Therefore the appropriate cycle length should be 1 year or shorter. This was the case in all studies, except for one study that used a cycle length of 5 years.[21]

Data identification
Several studies failed to describe their data sources in such detail that replication of the study using the same data would be possible.[21, 25, 26] Especially methods of deriving expert opinion and choices of data sources were unclear.

Data modelling: baseline data
Since TAVI is a relatively new treatment, (real-world) clinical effectiveness data are limited. Therefore many studies used the PARTNER trial as source for clinical data. This trial consists of two cohorts: PARTNER-A comparing TAVI with SAVR in high-risk operable patients[3] and PARTNER-B comparing TAVI with ST in inoperable patients.[4] Even though many studies used clinical data from these cohorts, there are considerable differences in resulting cost-effectiveness outcomes. Possible explanations for these differences are inclusion of other cost components or sources, other methods of extrapolation of survival or utilities beyond the follow-up time of the trial, variations in time horizon, different model structures, included complications, etcetera. [25, 26, 38, 39]The baseline characteristics of populations differed between studies, especially operable risk. Most studies comparing TAVI with ST included inoperable patients based on the PARTNER-B trial definition[23, 27-33], while patients in other studies were at lower operable risk.[2, 22, 25, 26] The latter studies had lower mean patient ages and less patients in NYHA class III/IV, but they did not report better cost-effectiveness outcomes.[2, 22, 25, 26]

Three studies comparing TAVI with SAVR included high-risk operable patients based on the PARTNER-A trial definition.[23, 24, 29] Other studies used slightly different definitions, resulting in the inclusion of patients with lower mean age, logistic EuroSCORE and/or proportion of patients in NYHA class III/IV.[2, 25, 26, 30] Most of these studies found that TAVI costs more, but gains more QALYs, while studies using the PARTNER-A trial definition found that TAVI is dominated by SAVR.

Besides differences between studies, there were differences in baseline characteristics between groups within studies that might have influenced the cost-effectiveness outcomes.[22, 30] For example, Orlando et al.[30] derived survival estimates from different sources with lower operable risks for SAVR patients compared to TAVI. Therefore SAVR patients survival may be overestimated, resulting in lower incremental QALY gains due to TAVI. Further, Neyt et al. [29] based costs of SAVR on patients with a lower surgical risk (i.e. >70 years with high severity of illness index, but not selected on operable risk) than the TAVI patients. This might explain the high incremental costs of TAVI in this study. In addition, there are unmeasured patient characteristics that are not considered in operable risk scores, such as patient frailty, that are important in treatment selection.[40] Consequently, this might have resulted in other unobservable differences in patient characteristics between SAVR and TAVI patients that may have influenced the results.

Data modelling: Treatment effects

The time horizon of most models included in this review is (equivalent to) lifetime, while the follow-up of the clinical trials that are used as input for mortality and complication rates is limited to a few years. Therefore, the included studies needed to make assumptions about survival beyond the trial data, or extrapolate the available data using survival analysis techniques. The extrapolation technique of survival data was reported in most studies (except for Beresniak et al. [21] and Gada et al. [25, 26]), but there was a lack of consistency in techniques between studies which might have influenced cost-effectiveness outcomes.

Three studies explicitly stated using separate parametric models to fit survival curves for TAVI versus ST because the proportional hazard assumption did not hold.[22, 30, 33] Brecker et al. [22] and Orlando et al. [30] used a Weibull distribution, but it was not reported which parametric function Watt et al. [33] used. The all-cause mortality increases faster over time in ST than TAVI patients [22], which might explain the relatively high incremental QALY gains of TAVI in these studies.[22, 30, 33]

Queiroga et al.[31] also fitted a Weibull distribution to the observed values, but it is unclear whether separate functions were fitted for both treatment groups. Further, Simons et al. [32] used a piecewise exponential curve accounting for higher mortality rates in ST during the first 6 months than the period thereafter, while other studies continued the trend of higher mortality beyond 6 months. This would result in a higher QALY gain after ST in Simons et al. compared to other studies, which was true for five of the other seven studies that reported LY or QALY gain after ST.[22, 27, 28, 30, 33]

Other studies seem to have assumed that the proportional hazard assumption was true from the time of the intervention until death. Fairbairn et al.[24] assumed the same constant proportional changes observed from year 1 to year 2 for the years beyond two years after the intervention. Hancock-Howard et al. [27] extrapolated the 1-, 6-, 12- and 24-month survival data from the PARTNER trial to 36 months using an exponential trend line function. Neyt et al. [29] assumed that the difference between life expectancy of TAVI and MM patients remained constant during the lifetime horizon of the model and after 1 year the monthly mortality rate increased according to age- and sex- adjusted mortality rates of the general population. As expected, these studies reported smaller incremental QALY differences compared to studies using separate parametric models for different treatments.[22, 30, 33]

Doble et al. [23] based the mortality rates from 2 to 20 years after the intervention on Canadian life tables. This means that they assume that the intervention has no continuing effect beyond two years after the intervention. This might explain the small difference in life years after SAVR and TAVI found in this study (0.01 LY).

Two studies modelled the mortality rate by multiplying the age- and sex-adjusted mortality rates of the general population with 1.5 to represent higher than average mortality risk in TAVI patients, whereas the life expectancy of MM patients was assumed to be 3 years.[2, 28] This means that the mortality rate in TAVI patients was 50% higher than the average population, which might explain the low incremental QALY gain reported in (high-risk subgroup of) these studies.

Data modelling: Costs

Most studies discounted costs and effects according to national economic evaluation guidelines, but there were four studies that did not report if and how costs and effects were discounted.[21, 25, 26, 28] Discount rates did not seem to influence cost-effectiveness outcomes much, suggesting other differences between studies had a larger impact on results.

There has been much debate on including costs unrelated to the disease or intervention of interest during life years gained.[41] Simons et al. [32] was the only study that included additional healthcare costs unrelated to aortic stenosis or its treatment and management. Since the hazard rate of death is higher in patients in NYHA class I/II that received MM with BAV compared to TAVI[32], these additional healthcare costs are mostly accrued by TAVI patients. This might explain the relative high ICER found in this study. This finding is in line with another study that illustrated that including unrelated medical costs would increase the ICER of TAVI versus ST.[41]

Data modelling: Quality of life weights (utilities)

The way to translate PARTNER trial data to utilities differed between studies resulting in different utility estimates. Seven studies [2, 22-24, 28, 30, 33] calculated utilities based on utilities per NYHA class derived from other literature [42-45] multiplied with the proportion of patients in each NYHA class in the PARTNER trial. The NYHA class consists of four classes reflecting the patient's limitations during physical activity. In contrast with general quality of life instruments, the NYHA class is assessed by clinicians instead of patients and does not consider social and mental/emotional aspects of quality of life. [46] In addition, applying utilities by NYHA class might underestimate the uncertainty in utility estimates because a change in NYHA class is associated with a fixed change in utility similar for each patient. This might explain the relatively high incremental QALY gains due to TAVI in two studies [22, 33] that used relatively high fixed utility gains for each lower NYHA class, because one year after the intervention a larger proportion of TAVI patients compared to ST patients was in a lower NYHA class.[4] Furthermore, utility estimates varied substantially between sources; not only in absolute value for the same NYHA class, but also in the differences between NYHA classes.[47] Therefore, indirect utility assessment using NYHA class is inappropriate and direct utility assessment using preference-based quality of life instruments is preferred. However, we found no clear difference in utility estimates based on NYHA classes or EQ-5D measurements.

There were several other assumptions about utilities that might have influenced cost-effectiveness outcomes of the studies. For example, Orlando et al. [30] made a distinction between utilities of TAVI survivors with and without rehospitalisation, that was not applied to MM patients. Therefore, TAVI patients without rehospitalisation could gain more QALYs than MM patients without rehospitalisation. This might explain the relative high incremental QALY gain due to TAVI found in this study.

Assessment of uncertainty

The quality of a decision-analytic model does not only depend on the methods of determining the point estimate of the ICER, but also on how uncertainty surrounding this outcome is considered.[48] Parameter and structure uncertainty were most often addressed, but most studies could be improved by also considering methodological uncertainty and heterogeneity. Only six studies reported information on statistical significance (p-values or confidence intervals) of differences in costs and utilities.[21, 22, 25, 29, 32, 33] In all but one study [25] the differences were statistically significant. Twelve studies reported the probability of being cost-effective [2, 22-30, 32, 33] and nine studies supported these probabilities by publishing cost-effectiveness acceptability curves.[2, 23, 24, 27-30, 32, 33]

Consistency (i.e. validity)
The studies did not pay much attention to consistency of their models. Only three studies[2, 23, 32] reported testing the mathematical logic of their model (internal consistency, e.g. model replication with other software) and two studies calibrated their model against independent data (external consistency).[29, 32] Further, about half of the studies did not compare their results with previous decision-analytic models.[2, 21, 25, 26, 28, 31, 33] However, when studies were published before 2012 we assumed that it was not possible to compare with previous studies because they did not exist or were published during the time of the study.[2, 21, 25, 26]

Opportunities for future economic models
This review revealed several opportunities for future economic models regarding heart valve implantations.

Firstly, gaps in the literature on model-based economic evaluations of heart valve implantations can be filled by evaluating cost-effectiveness of heart valve implantations in valve positions other than the aortic valve and by comparing the cost-effectiveness of SAVR with mechanical or biological valves. Both valve types have their own strengths and limitations and there are differences in healthcare use which might influence cost-effectiveness. Further, it would be interesting to investigate how including costs outside of healthcare (societal perspective), such as productivity and informal care costs, would influence the cost-effectiveness of heart valve implantations.

Secondly, there are methodological alternatives to the frequently used decision trees and Markov models, such as patient-simulation models. Advantages of patient-simulation models are their ability to incorporate recurrent events and to 'remember patient history' without producing unmanageable numbers of health states, resulting in greater flexibility in examining the impact of patient characteristics on outcomes.[36, 49]

Thirdly, improvements can be made in the methodological quality of studies by describing and justifying chosen methods and data sources in more detail, performing sensitivity analysis on extrapolation of results, performing subgroup analyses, and considering methodological and structural uncertainty and consistency (i.e. validity) of the model.

Finally, in this review only two studies used real-world data from patient registries instead of clinical trials.[21,22] In the future, we expect more model-based cost-effectiveness studies using data from patient registries including TAVI patients. However, the comparison of TAVI and ST in these registries will become increasingly

difficult because of the positive results of TAVI in inoperable patients of the PARTNER-B trial, which make it unethical to deny TAVI in these patients. This will lead to serious selection bias in registry data. In that case, using a historical cohort of ST patients, for example as in Freeman et al.[35], might better reflect real-world outcomes in ST.

Limitations

This study has several limitations. Firstly, we experienced difficulties in using the Philips checklist to assess the methodological quality of the studies. Some criteria are umbrella-criteria that should be assessed differently for different types of data (i.e. utilities, costs, etc.). For many criteria the methods were described but not explained or justified. In these cases we decided that the study fulfilled the criteria but we added a remark that there was no justification reported. Sometimes criteria were partially fulfilled which made it difficult to decide if the criteria should be assessed as fulfilled or not. Therefore, we did not exclude studies with low scores on the Philips checklist. Secondly, it was often difficult to fully understand the details of a decision-analytic model because of space limits on papers.

CONCLUSION

This review provided an overview of the existing decision-analytic models regarding the cost-effectiveness of heart valve implantations. Our results showed that in most studies TAVI was cost-effective compared to ST in inoperable and high-risk operable patients and in all studies SAVR was cost-effective compared to ST in operable patients, but the results were not consistent on the cost-effectiveness of TAVI versus SAVR in high-risk operable patients. This review showed that future models can improve their methodological quality and that there is room for patient-simulation models considering the cost-effectiveness of heart valve implantations in other valve positions besides the aortic valve, performed from a societal perspective.

Acknowledgements. We thank Wichor Bramer, information specialist at the Medical Library of the Erasmus University Medical Center, for his help with drafting the search query and executing the systematic literature retrieval.

Funding. We acknowledge the financial support from the Netherlands Cardio Vascular Research Initiative: the Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences.

Conflicts of interest. None.

REFERENCES

1. Wu, Y., et al., *Cost-effectiveness of aortic valve replacement in the elderly: an introductory study.* The Journal of thoracic and cardiovascular surgery, 2007. 133(3): p. 608-613.
2. Scottish Health Technologies Group (SHTG). *Evidence Development Pilot Project:Transcatheter Aortic Valve Implantation in Scotland*. 2010 [cited 2015 June]; Available from: http://www.gla.ac.uk/media/media_218806_en.pdf.
3. Smith, C.R., et al., *Transcatheter versus surgical aortic-valve replacement in high-risk patients.* New England Journal of Medicine, 2011. **364**(23): p. 2187-2198.
4. Leon, M.B., et al., *Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery.* New England Journal of Medicine, 2010. **363**(17): p. 1597-1607.
5. National Institute for Health and Care Excellence, *Transcatheter aortic valve implantation for aortic stenosis. NICE interventional procedure guidance [IPG421]*. 2012, NICE.
6. Reynolds, M.R., et al., *Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B).* Circulation, 2012. **125**(9): p. 1102-1109.
7. Reynolds, M.R., et al., *Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A).* Journal of the American College of Cardiology, 2012. **60**(25): p. 2683-2692.
8. Philips, Z., et al., *Review of guidelines for good practice in decision-analytic modelling in health technology assessment.* Health Technology Asses., 2004. **8**(36): p. 1-172.
9. Huygens, S.A., et al., *Conceptual model for early health technology assessment of current and novel heart valve interventions.* Open Heart, 2016. **3**(2): p. e000500.
10. Roberts, M., et al., *Conceptualizing a model. A report of the ISPOR-SMDM Modeling Good Research Practices Task Force–2.* Medical Decision Making, 2012. **32**(5): p. 678-689.
11. Iannaccone, A. and T.H. Marwick, *Cost effectiveness of transcatheter aortic valve replacement compared with medical management or surgery for patients with aortic stenosis.* Applied health economics and health policy, 2015. **13**(1): p. 29-45.
12. Eaton, J., et al., *Is transcatheter aortic valve implantation (TAVI) a cost-effective treatment in patients who are ineligible for surgical aortic valve replacement? A systematic review of economic evaluations.* Journal of medical economics, 2014. **17**(5): p. 365-375.
13. Indraratna, P., et al., *Systematic review of the cost-effectiveness of transcatheter aortic valve implantation.* The Journal of Thoracic and Cardiovascular Surgery, 2014. **148**(2): p. 509-514.
14. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* Annals of internal medicine, 2009. **151**(4): p. W-65-W-94.
15. The World Bank, *The World Bank: Inflation, GDP deflator (annual %)*.
16. Organisation for Economic Co-operation and Development (OECD), *Purchasing Power Parities for GDP and related indicators. http://stats.oecd.org/*.

17. World Health Organization, *World Health Organization: Choosing Interventions that are Cost Effective (WHO-CHOICE)*. 2012, World Health Organization: Geneva.
18. Organisation for Economic Co-operation and Development (OECD). *Gross domestic product.* . 2016 2 January 2017]; Available from: http://stats.oecd.org/.
19. Drummond, M.F. and T.O. Jefferson, *Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party.* BMJ: British Medical Journal, 1996. **313**(7052): p. 275.
20. Evers, S., et al., *Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria.* International journal of technology assessment in health care, 2005. **21**(02): p. 240-245.
21. Beresniak, A., et al., *Cost-effectiveness of mitral valve repair versus replacement by biologic or mechanical prosthesis.* Ann Thorac Surg, 2013. **95**(1): p. 98-104.
22. Brecker, S., et al., *Cost-utility of transcatheter aortic valve implantation for inoperable patients with severe aortic stenosis treated by medical management: a UK cost-utility analysis based on patient-level data from the ADVANCE study.* Open heart, 2014. **1**(1): p. e000155.
23. Doble, B., et al., *Cost-effectiveness of the Edwards SAPIEN transcatheter heart valve compared with standard management and surgical aortic valve replacement in patients with severe symptomatic aortic stenosis: A Canadian perspective.* The Journal of Thoracic and Cardiovascular Surgery, 2013. **146**(1): p. 52-60. e3.
24. Fairbairn, T.A., et al., *The cost-effectiveness of transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis at high operative risk.* Heart, 2013. **99**(13): p. 914-920.
25. Gada, H., et al., *Markov model for selection of aortic valve replacement versus transcatheter aortic valve implantation (without replacement) in high-risk patients.* The American Journal of Cardiology, 2012. **109**(9): p. 1326-1333.
26. Gada, H., S. Agarwal, and T.H. Marwick, *Perspective on the cost-effectiveness of transapical aortic valve implantation in high-risk patients: Outcomes of a decision-analytic model.* Annals of Cardiothoracic Surgery, 2012. **1**(2): p. 145-155.
27. Hancock-Howard, R.L., et al., *Cost effectiveness of transcatheter aortic valve replacement compared to medical management in inoperable patients with severe aortic stenosis: Canadian analysis based on the PARTNER Trial Cohort B findings.* Journal of Medical Economics, 2013. **16**(4): p. 566-574.
28. Murphy, A., et al., *Transcatheter aortic valve implantation for severe aortic stenosis: the cost-effectiveness case for inoperable patients in the United Kingdom.* International Journal of Technology Assessment in Health Care, 2013. **29**(01): p. 12-19.
29. Neyt, M., et al., *A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population.* BMJ open, 2012. **2**(3).
30. Orlando, R., et al., *Cost-effectiveness of transcatheter aortic valve implantation (TAVI) for aortic stenosis in patients who are high risk or contraindicated for surgery: A model-based economic evaluation.* Health Technol Assess, 2013. **17**(33): p. 1-86.

31. Queiroga, M.A.C.Q., et al., *Transcatheter aortic valve implantation for the treatment of severe aortic valve stenosis in inoperable patients under th he Brazilian Supplemental health system - Cost-effectiveness analysis.* Rev Bras Cardiologia Invasia, 2013. **21**(3).
32. Simons, C.T., et al., *Transcatheter aortic valve replacement in nonsurgical candidates with severe, symptomatic aortic stenosis: a cost-effectiveness analysis.* Circulation: Cardiovascular Quality and Outcomes, 2013. **6**(4): p. 419-428.
33. Watt, M., et al., *Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement.* Heart, 2012. **98**(5): p. 370-376.
34. Cooper, N., et al., *Use of evidence in decision models: an appraisal of health technology assessments in the UK since 1997.* Journal of health services research & policy, 2005. **10**(4): p. 245-250.
35. Reardon, M.J., et al., *2-year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement.* Journal of the American College of Cardiology, 2015. **66**(2): p. 113-121.
36. Siebert, U., et al., *State-transition modeling: a report of the ISPOR-SMDM modeling good research practices task force-3.* Value in Health, 2012. **15**(6): p. 812-820.
37. Vahanian, A., et al., *Guidelines on the management of valvular heart disease (version 2012) The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS).* European Heart Journal, 2012. **33**(19): p. 2451-2496.
38. de Groot, S., et al., *Balancing the optimal and the feasible: A practical guide for setting up patient registries for the collection of real-world data for health care decision making based on Dutch experiences.* Value in Health, 2016. **20**(4): p. 627-636.
39. Freeman, P.M., et al., *Severe symptomatic aortic stenosis: medical therapy and transcatheter aortic valve implantation (TAVI)—a real-world retrospective cohort analysis of outcomes and cost-effectiveness using national data.* Open Heart, 2016. **3**(1): p. e000414.
40. Nishimura RA, O.C., Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD, *2014 AHA/ACC guideline for the management of patients with valvular heart disease.* Journal of the American College of Cardiology, 2014. **63**(22): p. 2438–88.
41. Baal, P., D. Meltzer, and W. Brouwer, *Future costs, fixed healthcare budgets, and the decision rules of cost-effectiveness analysis.* Health economics, 2016. **25**(2): p. 237-248.
42. Göhler, A., et al., *Utility estimates for decision–analytic modeling in chronic heart failure—Health states based on New York Heart Association Classes and number of rehospitalizations.* Value in Health, 2009. **12**(1): p. 185-187.
43. Fairbairn, T.A., et al., *Serial change in health-related quality of life over 1 year after transcatheter aortic valve implantation: predictors of health outcomes.* Journal of the American College of Cardiology, 2012. **59**(19): p. 1672-1680.
44. Maliwa, M.A., et al., *Quality of life and NYHA class 30 years after mechanical aortic valve replacement.* Vascular, 2003. **11**(5): p. 381-387.
45. Fox, M., et al., *The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.* Health Technol Assess., 2007. **11**(47): p. iii-iv, ix-248.

46. Van Geldorp, M.W.A., et al., *Quality of life among patients with severe aortic stenosis.* Netherlands Heart Journal, 2013. **21**(1): p. 21-27.
47. Brabandt van, H., et al. *Cardiac Resynchronisation Therapy: A Health technology Assessment*. KCE reports 145C 2010 [cited 2015 June]; Available from: https://kce.fgov.be/sites/default/files/atoms/files/kce_145c_cardiac_resynchronisation.
48. Briggs, A.H., et al., *Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6.* Value in Health, 2012. **15**(6): p. 835-842.
49. Karnon, J., et al., *Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–4.* Medical Decision Making, 2012. **32**(5): p. 701-711.
50. Wendt, D., et al., *Society of Thoracic Surgeons Score is superior to the EuroSCORE determining mortality in high risk patients undergoing isolated aortic valve replacement.* The Annals of Thoracic Surgery, 2009. **88**(2): p. 468-475.
51. Leontyev, S., et al., *Aortic valve replacement in octogenarians: utility of risk stratification with EuroSCORE.* The Annals of Thoracic Surgery, 2009. **87**(5): p. 1440-1445.
52. Cribier, A., et al., *Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience.* Journal of the American College of Cardiology, 2006. **47**(6): p. 1214-1223.
53. Linke, A., et al., *Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study.* European Heart Journal, 2014. **35**(38): p. 2672-2684.
54. Wenaweser, P., et al., *Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality.* Journal of the American College of Cardiology, 2011. **58**(21): p. 2151-2162.

SUPPLEMENTARY MATERIAL

Embase.com

('economic aspect'/exp OR (cost* OR econom* OR price):ab,ti) AND ('decision tree'/de OR 'decision support system'/de OR model/exp OR algorithm/de OR (model* OR (decisi* NEAR/3 (tree* OR rule* OR support* OR system*)) OR (concept* NEAR/3 framework*) OR simulat* OR algorithm*):ab,ti) AND ('heart valve'/de OR 'heart valve surgery'/de OR 'heart valve prosthesis'/exp OR 'heart valve replacement'/exp OR 'aorta valve'/de OR 'pulmonary valve'/de OR 'aorta stenosis'/exp OR 'heart valve stenosis'/de OR 'heart valve regurgitation'/de OR 'valvular heart disease'/de OR 'aorta valve disease'/exp OR 'pulmonary valve disease'/exp OR (((heart OR cardiac OR aort* OR pulmonar*) NEAR/3 valv*) OR ((aort* OR pulmonar*) NEAR/3 (steno* OR calcif* OR regurgitat*)) OR aortostenos*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OvidSP)

(((exp "economics"/ OR economics.xs. OR (cost* OR econom* OR price).ab,ti.) AND ("decision trees"/ OR "Decision Support Systems, Clinical"/ OR exp "Models, Theoretical"/ OR algorithms/ OR (model* OR (decisi* ADJ3 (tree* OR rule* OR support* OR system*)) OR (concept* ADJ3 framework*) OR simulat* OR algorithm*).ab,ti.)) OR exp "Models, Economic"/) AND ("heart valves"/ OR "Heart Valve Prosthesis"/ OR "Heart Valve Prosthesis Implantation"/ OR "Aortic Valve"/ OR "pulmonary valve"/ OR exp "Aortic Valve Stenosis"/ OR "Heart Valve Diseases"/ OR (((heart OR cardiac OR aort* OR pulmonar*) ADJ3 valv*) OR ((aort* OR pulmonar*) ADJ3 (steno* OR calcif* OR regurgitat*)) OR aortostenos*).ab,ti.) NOT (exp animals/ NOT humans/)

Cochrane

((cost* OR econom* OR price):ab,ti) AND ((model* OR (decisi* NEAR/3 (tree* OR rule* OR support* OR system*)) OR (concept* NEAR/3 framework*) OR simulat* OR algorithm*):ab,ti) AND ((((heart OR cardiac OR aort* OR pulmonar*) NEAR/3 valv*) OR ((aort* OR pulmonar*) NEAR/3 (steno* OR calcif* OR regurgitat*)) OR aortostenos*):ab,ti)

Web-of-science

TS=(((cost* OR econom* OR price)) AND ((model* OR (decisi* NEAR/3 (tree* OR rule* OR support* OR system*)) OR (concept* NEAR/3 framework*) OR simulat* OR algorithm*)) AND ((((heart OR cardiac OR aort* OR pulmonar*) NEAR/3 valv*) OR ((aort* OR pulmonar*) NEAR/3 (steno* OR calcif* OR regurgitat*)) OR aortostenos*)))

Scopus

TITLE-ABS-KEY(((cost* OR econom* OR price)) AND ((model* OR (decisi* W/3 (tree* OR rule* OR support* OR system*)) OR (concept* W/3 framework*) OR simulat* OR

algorithm*)) AND ((((heart OR cardiac OR aort* OR pulmonar*) W/3 valv*) OR ((aort* OR pulmonar*) W/3 (steno* OR calcif* OR regurgitat*)) OR aortostenos*)))

PubMed publisher

((((cost*[tiab] OR econom*[tiab] OR price[tiab])) AND ((model*[tiab] OR (decisi*[tiab] AND (tree*[tiab] OR rule*[tiab] OR support*[tiab] OR system*[tiab])) OR (concept*[tiab] AND framework*[tiab]) OR simulat*[tiab] OR algorithm*[tiab]))))) AND ((((heart[tiab] OR cardiac[tiab] OR aort*[tiab] OR pulmonar*[tiab]) AND valv*[tiab]) OR ((aort*[tiab] OR pulmonar*[tiab]) AND (steno*[tiab] OR calcif*[tiab] OR regurgitat*[tiab])) OR aortostenos*[tiab])) AND publisher[sb]

Google Scholar

Economy|Economic|economical|economically|economics|cost|costs|model|algorithm|"decision|tree|rule|support|system"|"conceptual|framework"|simulation|"aorta|aortic|heart|cardiac|pulmonary|valve|valves|stenosis|regurgitation"

Extracted data

Study characteristics:

- Target population,
- Patient characteristics,
- Valve position,
- Intervention of interest and comparator(s),
- Location (i.e. country),
- Study perspective.

Model characteristics:

- Type of decision-analytic model,
- Model health states,
- Health outcomes,
- Time horizon,
- Cycle length (in Markov models),
- Discount rates.

Cost-effectiveness outcomes:

- Costs per treatment option,
- Effects per treatment option,
- Prosthetic valve prices,
- Incremental costs,
- Incremental effects,
- Incremental cost-effectiveness ratios (ICER).

Table S1. Philips checklist.

	SHTG 2010	Gada 2012a	Gada 2012b	Neyt 2012	Watt 2012	Beresniak 2013	Doble 2013	Fairbairn 2013	Hancock-Howard 2013	Murphy 2013	Orlando 2013	Queiroga 2013	Simons 2013	Brecker 2014	**Total**	%
Structure																
Statement of decision problem and objective																
Is there a clear statement of the **decision problem**?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**8**	100
Is the **objective** of the evaluation and model specified and consistent with the stated decision problem?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Is the primary **decision-maker** specified?	1	0	0	1	1	1	1	1	1	1	1	1	0	1	**11**	79
Statement of scope and perspective																
Is the **perspective** of the model stated clearly?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Are the **model inputs** consistent with the stated perspective?	1	1	1	1	1	1	1	1	1	1	1	1	0	1	**13**	93
Has the **scope** of the model been stated and justified?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Are the **outcomes** of the model consistent with the perspective, scope and overall objective of the model?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Rationale for structure																
Is the structure of the model consistent with a **coherent theory of the health condition** under evaluation?	1	1	1	1	1	1	1	0	1	1	1	0	1	1	**12**	86
Are the **sources of data** used to develop the structure of the model specified?	0	0	0	0	1	0	0	0	0	0	0	0	1	1	**3**	21
Are the **causal relationships** described by the model structure justified appropriately?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Structural assumptions																
Are the structural assumptions **transparent and justified**?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Are the structural assumptions **reasonable** given the overall objective, perspective and scope of the model?	0	0	0	1	0	1	1	0	1	1	0	1	1	1	**8**	57
Strategies and comparators																
Is there a clear **definition of the options** under consideration?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Have **all feasible and practical options** been evaluated?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Is there **justification for the exclusion** of feasible options?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**-**	-
Model type																
Is the chosen **model type** appropriate given the decision problem and specified causal relationships within the model?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Time horizon																
Is the **time horizon** of the model sufficient to reflect all important differences between options?	1	1	1	1	1	1	1	1	0	1	1	0	1	0	**11**	79

Table S1. Continued

	SHTG 2010	Gada 2012a	Gada 2012b	Neyt 2012	Watt 2012	Beresniak 2013	Doble 2013	Fairbairn 2013	Hancock-Howard 2013	Murphy 2013	Orlando 2013	Queiroga 2013	Simons 2013	Brecker 2014	**Total**	%
Are the time horizon of the model, the duration of treatment and the duration of treatment effect **described and justified**?	1	0	0	1	1	1	1	1	1	1	1	0	1	1	**11**	79
Disease pathways																
Do the disease states (state transition model) or the pathways (decision tree model) **reflect the underlying biological process** of the disease in question and the impact of the intervention?	1	1	1	1	1	1	1	1	1	1	1	0	1	1	**13**	93
Cycle length																
Is the **cycle length** defined and justified in terms of the natural history of the disease?	1	1	1	1	1	0	1	1	-	1	-	1	1	1	**11**	92
Data																
Data identification																
Are the **data identification methods** transparent and appropriate given the objectives of the model?	1	0	0	1	1	0	1	1	1	1	1	1	1	1	**11**	79
Where **choices** have been made **between data sources**, are these justified appropriately?	0	0	0	0	1	0	0	1	1	1	1	0	0	1	**6**	43
Has **particular attention** been paid to identifying data for the **important parameters** in the model?	1	0	0	1	1	0	1	1	1	1	1	1	1	1	**11**	79
Has the **quality of the data** been assessed appropriately?	1	0	1	1	1	0	1	1	1	1	1	1	1	1	**12**	86
Where **expert opinion** has been used, are the methods described and justified?	0	-	-	0	0	-	-	-	0	-	0	0	-	-	**0**	0
Data modelling																
Is the data modelling methodology based on **justifiable statistical and epidemiological techniques**? (specific issues to consider include those listed below)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Baseline data																
Is the **choice of baseline data** described and justified?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Are **transition probabilities** calculated appropriately?	1	1	1	1	0	0	1	0	0	1	1	0	1	1	**9**	64
Has a **half-cycle correction** been applied to both cost and outcome?	-	-	-	0	-	-	0	-	-	-	-	0	-	0	**0**	0
If not, has this omission been justified?	-	-	-	0	-	-	0	-	-	-	-	0	-	0	**0**	0
Treatment effects																
If relative treatment effects have been derived from **trial data**, have they been **synthesised** using appropriate techniques?	-	0	0	-	-	-	-	-	-	-	-	-	-	-	**0**	0
Have the methods and assumptions used to **extrapolate short-term results to final outcomes** been documented and justified?	1	0	0	1	1	0	1	1	1	1	1	1	1	1	**11**	79
Have alternative assumptions been explored through sensitivity analysis?	0	0	0	0	1	0	1	0	0	0	0	0	1	1	**4**	29

Table S1. Continued

	SHTG 2010	Gada 2012a	Gada 2012b	Neyt 2012	Watt 2012	Beresniak 2013	Doble 2013	Fairbairn 2013	Hancock-Howard 2013	Murphy 2013	Orlando 2013	Queiroga 2013	Simons 2013	Brecker 2014	**Total**	%
Have assumptions regarding the **continuing effect of treatment once treatment is complete** been documented and justified?	1	0	0	1	0	0	1	1	1	1	1	0	1	1	**9**	64
Have alternative assumptions been explored through sensitivity analysis?	0	1	1	1	1	0	1	1	0	1	1	0	0	1	**9**	64
Costs																
Are the **costs** incorporated in the model justified?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**14**	100
Has the **source** for all costs been described?	1	1	1	1	0	0	1	1	1	0	1	0	1	1	**10**	71
Have **discount rates** been described and justified given the target decision-maker?	1	0	0	1	1	0	1	1	1	0	1	1	1	1	**10**	71
Quality of life weights (utilities)																
Are the **utilities** incorporated into the model appropriate?	1	1	1	1	1	-	1	1	1	1	1	-	1	1	**12**	100
Is the **source** for the utility weights referenced?	1	1	1	1	1	-	1	1	1	1	1	-	1	1	**12**	100
Are the methods of **derivation for the utility weights** justified?	0	1	1	1	0	-	0	1	1	0	0	-	1	0	**6**	50
Data incorporation																
Have all **data** incorporated into the model been **described and referenced** in sufficient detail?	0	0	0	1	0	0	1	1	1	0	1	0	0	1	**6**	43
Has the use of **mutually inconsistent data** been justified (i.e. are assumptions and choices appropriate)?	-	-	-	1	-	-	-	-	-	-	-	-	-	1	**2**	100
Is the **process of data incorporation** transparent? (i.e. Is it clear whether data are incorporated as point estimate or distribution (+ justification for choice of distribution)?)	1	0	1	1	1	0	1	1	0	1	1	0	1	1	**10**	71
If data have been incorporated as **distributions,** has the choice of distribution for each parameter been described and justified?	0	1	1	1	0	0	1	0	0	1	1	1	1	1	**9**	64
If data have been incorporated as distributions, is it clear that **second order uncertainty is reflected?**	1	1	1	1	1	-	1	1	-	1	1	1	1	1	**12**	100
Assessment of uncertainty																
Have the **four principal types of uncertainty** been addressed?	0	0	0	1	0	0	0	0	0	0	0	0	0	0	**1**	7
If not, has this omission of particular forms of uncertainty been justified?	0	0	0	-	0	0	0	0	0	0	0	0	0	0	**0**	0
Have **methodological uncertainties** been addressed by running alternative versions of the model with different methodological assumptions?	0	0	0	1	0	0	0	1	0	0	0	1	0	0	**3**	21
Is there evidence that **structural uncertainties** have been addressed via sensitivity analysis?	0	0	0	1	1	1	1	1	1	0	0	1	0	1	**8**	57
Has **heterogeneity** been dealt with by running the model separately for different subgroups?	0	0	0	1	0	0	0	0	0	0	1	0	1	1	**4**	29

Table S1. Continued

	SHTG 2010	Gada 2012a	Gada 2012b	Neyt 2012	Watt 2012	Beresniak 2013	Doble 2013	Fairbairn 2013	Hancock-Howard 2013	Murphy 2013	Orlando 2013	Queiroga 2013	Simons 2013	Brecker 2014	**Total**	%
Are the methods of assessment of **parameter uncertainty** appropriate?	1	1	1	1	0	1	1	1	1	1	1	1	1	1	**13**	93
If data are incorporated as **point estimates**, are the **ranges used for sensitivity analysis** stated clearly and justified?	-	0	0	1	1	0	1	1	1	0	1	1	1	1	**9**	69
Consistency																
Internal consistency																
Is there evidence that the **mathematical logic of the model** has been tested thoroughly before use?	1	0	0	0	0	0	1	0	0	0	0	0	1	0	**3**	21
External consistency																
Are any **counterintuitive results** from the model explained and justified?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**-**	-
If the model has been **calibrated against independent data**, have any differences been explained and justified?	0	0	0	1	0	0	0	0	0	0	0	0	1	0	**2**	14
Have the results of the model been **compared with those of previous models** and any differences in results explained?	-	-	-	1	0	-	1	1	1	0	1	0	1	1	**7**	70
Total score (not corrected for N/A)	34	27	29	46	35	22	42	39	35	35	39	28	41	44		
Number of items not applicable	8	7	7	4	6	12	5	7	8	7	7	7	7	4		
Total score, % (corrected for N/A)	69	54	58	87	69	49	81	78	71	70	78	56	82	83		

1 = criteria is fulfilled, 0 = criteria is not fulfilled, and '-' criteria is not applicable (NA).

Explanation for underlined scores:
Time horizon: Brecker: Time horizon in base-case analysis is 5 years, which is not equivalent to lifetime in this patient group. However, a sensitivity analysis with a time horizon of 10 years (=equivalent to lifetime) was performed. Neyt: This criteria is fulfilled in the subgroup of inoperable patients, but not for the subgroup of high-risk operable patients where the time horizon was only one year.
Disease pathways: Watt and Brecker: Health states based on location of care, reoperations and post-hospital rehabilitations, therefore it is only clear that they consider reoperations as complications. Faibairn and Simons: NYHA classes are not appropriate health states.
Data identification: Hancock-Howard: Only for the data sources on costs.
Baseline data: Brecker, Neyt and Queiroga: Not reported, therefore unclear if this was done.
Quality of life (weights): Neyt: This criteria is fulfilled in the subgroup of inoperable patients (where utilities are based on EQ-5D measurements), but not for the high-risk operable group.
Data incorporation: Queiroga: Distribution only defined for costs.

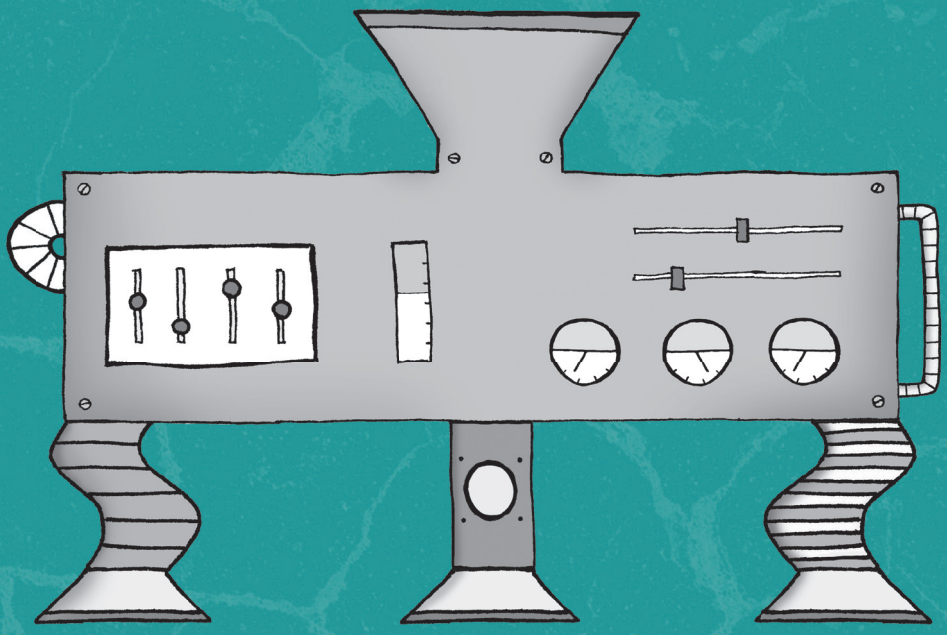
Table S2. Data sources and outcomes.

Author	Mortality	Baseline clinical data	Resource use	Costs	Utilities
SHTG 2010	Revive trials	Revive trials	NR	Previously published studies	NYHA class utilities [44] applied to Revive trials NYHA class proportions
Gada 2012a	Existing registries	Existing registries	Previously published studies	Previously published studies	PARTNER trial, measured with EQ-5D
Gada 2012b	Existing registries	Existing registries	Previously published studies	Previously published studies	PARTNER trial, measured with EQ-5D
Neyt 2012	PARTNER trial	PARTNER trial	Aggregated cost data of TAVI patients and data on hospital stays after surgical AVR complemented with APR-DRG costs	Aggregated cost data of TAVI patients and data on hospital stays after surgical AVR complemented with APR-DRG costs	Measured with EQ-5D in PARTNER trial for inoperable patients and based on assumptions for high-risk operable patients
Watt 2012	PARTNER trial	PARTNER trial	Expert opinion and literature review	British National Formulary, other publicly available national databases	NYHA class utilities [45] applied to PARTNER trial NYHA class proportions
Beresniak 2013	Cohort study	NR	Resource utilization survey	French medical information system program using national charge table and DRG coding	N/A
Doble 2013	PARTNER trial	PARTNER trial	NR	Ontario Case Costing Initiative	NYHA class utilities [42] applied to PARTNER trial NYHA class proportions
Fairbairn 2013	PARTNER trial	PARTNER trial	NR	NHS tariff payment by results fee and further costs calculated based on previously published hospitalization annual hazard per NYHA category	NYHA class utilities [43] applied to PARTNER trial NYHA class proportions combined with additional utility decrements for complications
Hancock-Howard 2013	PARTNER trial	PARTNER trial	Ontario Health Insurance Plan fee schedule and the Ontario Case Costing Initiative database	Ontario Health Insurance Plan fee schedule, the Ontario Case Costing Initiative database, and adjusted from French economic model	PARTNER trial, measured with EQ-5D
Murphy 2013	PARTNER trial	PARTNER trial	Previously published studies	Previously published studies	NYHA class utilities [44] applied to PARTNER trial NYHA class proportions
Orlando 2013	PARTNER trial	NR	NR	South Central report, NHS reference costs and previously published studies	NYHA class utilities [44] applied to PARTNER trial NYHA class proportions

Table S2. Continued

Author	Mortality	Baseline clinical data	Resource use	Costs	Utilities
Queiroga 2013	PARTNER trial	PARTNER trial	Based on data from a pre-planned economic study, conducted in parallel with the PARTNER trial	Based on data from a pre-planned economic study, conducted in parallel with the PARTNER trial	N/A
Simons 2013	PARTNER trial	PARTNER trial	NR	Medicare data and previously published studies	Medical Expenditure Panel Survey data
Brecker 2014	ADVANCE and PARTNER trial	ADVANCE and PARTNER trial	ADVANCE trial	British National Formulary, other publicly accessible databases and previously published studies	ADVANCE trial, measured with EQ-5D[53] (TAVI) and NYHA class utilities [45] applied to PARTNER trial NYHA class proportions (ST)

NR: not reported. APR-DRG: all patient refined diagnosis related groups. ICU: intensive care unit. SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve replacement. TF: transfemoral. TA: transapical. MM: medical management. ST: standard therapy; including MM and/or balloon aortic valvuloplasty (BAV). NYHA class: New York Heart Association class. PARTNER: Placement of Aortic Transcatheter Valves.[3, 4] REVIVE: The Registry of Endovascular Implantation of Valves in Europe trial started in 2003 in a single centre in France with the aim to study the feasibility and safety of TAVI in inoperable patients.[52] ADVANCE: Multicentre, non-randomized study that included 44 centres in 12 countries evaluating the outcomes of a self-expanding transcatheter aortic valve system in patients considered inoperable or at a higher surgical risk.[53]



3

Conceptual model for early health technology assessment of current and novel heart valve interventions

Simone A. Huygens, Maureen P.M.H. Rutten-van Mölken, Jos A. Bekkers, Ad J.J.C Bogers, Carlijn V.C. Bouten, Steven A.J. Chamuleau, Peter P.T. de Jaegere, Arie Pieter Kappetein, Jolanda Kluin, Nicolas M.D.A. van Mieghem, Michel I.M. Versteegh, Maarten Witsenburg, Johanna J.M. Takkenberg.

Open Heart. 2016;3:e000500.

ABSTRACT

Objective. The future promises many technological advances in the field of heart valve interventions, like tissue-engineered heart valves (TEHV). Prior to introduction in clinical practice it is essential to perform early Health Technology Assessment. We aim to develop a conceptual model that can be used to investigate the performance and costs requirements for TEHV to become cost-effective.

Methods. After scoping the decision problem, a workgroup developed the draft conceptual model based on clinical guidelines. This model was compared with existing models for cost-effectiveness of heart valve interventions, identified by systematic literature search. Next, it was discussed with a Delphi panel of cardiothoracic surgeons, cardiologists and a biomedical scientist (n=10).

Results. The conceptual model starts with the valve implantation. If patients survive the intervention, they can remain alive without complications, die from non-valve-related causes or experience a valve-related event. The events are separated in early and late events. After surviving an event, patients can experience another event or die due to non-valve-related causes. Predictors will include age, gender, NYHA class, left ventricular function, and diabetes. Costs and quality adjusted life years are to be attached to health conditions to estimate long-term costs and health outcomes.

Conclusion. We developed a conceptual model that will serve as foundation of a decision-analytic model that can estimate the potential cost-effectiveness of TEHV in early development stages. This supports developers in deciding about further development of TEHV and identifies promising interventions that may result in faster take-up in clinical practice by clinicians and reimbursement by payers.

INTRODUCTION

Heart valve disease represents a major global health burden. The prevalence of heart valve disease in the USA in 2000 was 2.5%.[1] The most common intervention for heart valve disease is surgical valve replacement with mechanical or biological heart valve substitutes. There is no perfect heart valve substitute as every heart valve substitute type has its own limitations.[2] The future promises many emerging technologies in the field of heart valve interventions. For example, tissue-engineered heart valves that are expected to be introduced in clinical practice in the next decade.[3, 4]

The scarcity of resources for healthcare implies that choices must be made regarding healthcare spending on current and novel heart valve interventions. This problem will only become more important in the future, since it is expected that healthcare costs will continue to rise due to ageing populations and development of new medical technologies.[5] Health Technology Assessment (HTA) can support healthcare decision makers in allocating the limited resources in a way that maximizes the health of the overall population and avoids implementation of comparatively ineffective or inefficient interventions.[6] Currently, the cost-effectiveness is often evaluated when the new intervention is ready for introduction in clinical practice to demonstrate healthcare payers that the new intervention is good value for money. However, at that time it may be too late to change the technology to better fit the needs of clinical practice in light of already existing treatment options. To avoid wasting large research and development (R&D) investments, developers should already ask themselves questions like: "What properties should the new technology minimally have to improve clinical outcomes in patients?" and "What are the maximum additional costs of the new technology compared to current treatments in order for the new technology to become cost-effective?" early in the development process. Early HTA is a form of HTA that evaluates technologies in development to support biomedical developers in maximizing the return on investment and societal impact of the new technology. [7] This could improve the pace and the efficiency of the development and guarantee successful implementation of the new technology in clinical practice in the future.[8]

This research is part of the Netherlands Cardio Vascular Research Initiative (CVON) 1Valve consortium that aims to develop the first in-human tissue-engineered heart valves. To support the developers in development of tissue-engineered heart valves, we are in the process of developing a decision-analytic model for the early HTA of tissue-engineered heart valves. In a decision-analytic model evidence from different sources on health outcomes, health-related quality of life and societal costs can be combined. The appropriate development of a decision-analytic model begins with

understanding the problem that is being represented by defining a conceptual model (CM).[9] This study describes the process of developing the CM for early HTA of novel heart valve interventions, especially tissue-engineered heart valves.

METHODS

The development of the CM was based on recommendations from ISPOR-SMDM Modeling Good Research Practices Task Force-2.[9] Figure 1 provides a schematic overview of the CM development process described in this paper. First, we scoped the decision problem and developed a draft CM. Next, we performed a systematic literature review to compare the structure of the draft CM with existing decision-analytic models. Finally, we organized a Delphi panel to validate the CM with experts and finalise the model.

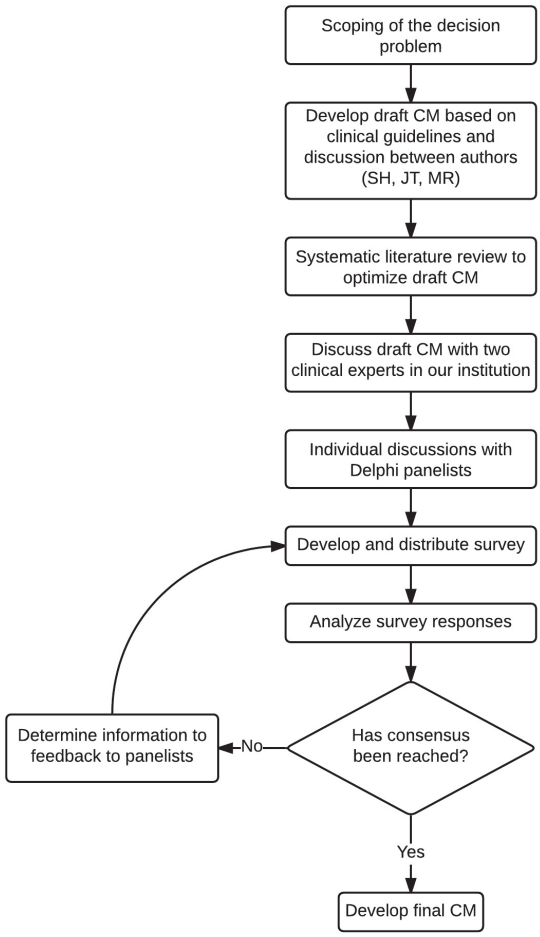


Figure 1. Schematic overview of the development process of the conceptual model. CM: conceptual model.

Scoping and draft conceptual model

It is important to elucidate the nature of the problem under consideration, modelling objectives, and scope before constructing the model.[9] Therefore, the problem definition, patient population, current treatment options, perspective, outcomes and time horizon were defined within a small workgroup (SH, MR, JT). Subsequently, the workgroup developed a draft CM using literature and clinical guidelines. Possible predictors of health outcomes were derived from The Working Group on Valvular Heart Disease of the European Society of Cardiology[10] and the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease.[11]

Literature review

The complete methods of the systematic review of existing decision-analytic models on the cost-effectiveness of heart valve interventions will be reported elsewhere. In short, in May 2015, several databases were searched using key words regarding economic evaluations, models, heart valve disease and implantations. Publications were included when they reported model-based economic evaluations considering costs and health outcomes of heart valve implantations. Papers solely describing regression models, cost-analyses, non-English publications, conference proceedings or abstracts, editorials and letters to the editor were excluded. References of the selected papers and previous systematic reviews were crosschecked for other relevant studies.

For the purpose of the development of the CM, study and model characteristics of included studies were extracted. Study characteristics included target population, patient characteristics, valve position, intervention of interest and comparator(s), location (i.e. country), and study perspective. Model characteristics included type of decision-analytic model, model health states, health outcomes, time horizon, cycle length (in Markov models), and discount rates. Additionally, we extracted cost-effectiveness results and critically appraised the methodological quality of the studies, but these results will be reported elsewhere.

Expert opinion

To assess whether the events and treatment options in the model represents clinical practice, we presented the CM to experts. This process was divided into two parts.

First, we discussed the draft CM with a cardiothoracic surgeon and intervention cardiologist in our hospital. The following topics were discussed: general understanding and completeness of the model, overlap between model elements, consideration of valve-related events on the short and/or long term, and combining valve-related events in composite events. Afterwards, we adapted the structure of the model based on the input of the experts.

Second, we gathered opinions of eight other experts from our (n=4) and other hospitals in the Netherlands (n=4) using a Delphi panel.[12] Altogether, the Delphi panel consisted of 10 panellists: 5 cardiothoracic surgeons, 4 cardiologists and 1 biomedical scientist. In the first round of the Delphi panel, we held individual semi-structured interviews with the panellists to explain the structure of the model, to discuss the events included in the model, and their typical treatment options, and to discuss subjects that emerged as a results of our systematic literature review. After the experts were interviewed, we converted the collected information into an online questionnaire. The first questionnaire asked panellists about their opinion on subjects other panellists brought up during the interviews. Based on the results of the first questionnaire, we have sent the panellists a second online questionnaire with an updated CM with explanation of the adaptions that were made. This round provided a final opportunity for the Delphi panellists to give suggestions about the CM.

RESULTS

Scoping and draft conceptual model

Problem definition

We defined the decision problem underlying our model as the choice of a heart valve intervention that results in the most health benefits for specific subgroups of patients at acceptable costs.[2] This includes current and novel heart valve interventions that are being developed and may be introduced in clinical practice in the future. One promising innovation is the development of tissue-engineered heart valves. In situ tissue-engineering provides a promising method where a synthetic biodegradable scaffold in the shape of a valve will be implanted in the patient. The scaffold recruits endogenous cells from the bloodstream and surrounding tissues, the cells form new tissue and gradually transform into a valve.[3]. These valves are foreseen to have important advantages: they will respond to patient growth, repair themselves and last a lifetime in the same way as most native valves do.[4]

Patients

The patient population of interest includes patients with severe valve stenosis or regurgitation in the aortic or pulmonary position that are deemed candidates for surgical valve replacement or transcatheter valve implantation. We focus on the aortic and pulmonary position because tissue-engineered heart valves, are expected to be implanted in these valve positions in the near future.

Current treatment options

The current treatment options are defined as surgical valve replacement and transcatheter valve implantation in the aortic or pulmonary valve position. To limit the complexity of the model and data requirements, valve repairs are not taken into account.

The choice of intervention and its outcomes in patients with heart valve disease differs substantially among age groups. To account for these differences, the study population is divided into four age subgroups: 0-18, 19-60, 61-70 and >70 years. The model structure is the same across subgroups, but the treatment options differ and input parameters are to be estimated separately for each age group and valve position. The following age-related considerations were taken into account in defining the age subgroups and corresponding treatment options. In children, the choice of heart valve substitute to use in surgical valve replacement is difficult because most heart valve substitutes are not able to respond to the patient's growth. This is not the case after the Ross procedure (i.e. pulmonary autograft), which may be an alternative for surgical valve replacement with bioprostheses or mechanical valves in patients with aortic valve disease.[13] In addition, pulmonary percutaneous valve intervention is a less invasive alternative for patients who developed dysfunction of the right ventricular outflow tract following neonatal repair of complex congenital heart disease.[14] In young adults, surgical valve replacement with a mechanical valve is generally preferred over bioprostheses because of its longer durability and subsequent lower risk of reoperation.[2] For middle aged patients, surgical valve replacement with biological or mechanical valves are both acceptable.[2] In elderly, bioprostheses are generally preferred because the patients' life expectancy is usually shorter than the durability of the valve and, therefore, they can benefit from the advantages of bioprostheses, such as no need for lifelong anticoagulation.[2] In elderly patients with severe aortic valve disease and a high surgery risk or for those who are not deemed operable because of comorbidities, transcatheter aortic valve implantation (TAVI) may be an alternative.[15]

Perspective, outcomes and time horizon

We chose a societal perspective, which means that all relevant costs and benefits are to be taken into account regardless of who bears the costs or enjoys the benefits.[16] The outcome measures were defined as health-related quality of life, event occurrence, event-free survival, valve-related and non-valve related mortality and societal costs. We decided to adopt a lifetime horizon, modelling outcomes from the start of the intervention until the patient dies.

Predictors of outcomes

We identified the following potentially relevant predictors of in-hospital events and mortality in patients with heart valve disease: age, gender, symptomatic status (New York Heart Association class), left ventricular ejection fraction, pulmonary artery systolic pressure, creatinine, chronic pulmonary disease, extracardiac arteriopathy, neurological impairment affecting daily activity, concomitant coronary artery disease, concomitant coronary artery bypass surgery, type of valve surgery, concomitant surgery of the ascending aorta, redo cardiac surgery, emergency surgery, frailty, major organ system dysfunction, and procedure-specific impediments (for example patients with a porcelain aorta are not suitable for TAVI).[10 11].

Draft conceptual model

The draft CM of patient prognosis after heart valve implantation is presented in Figures 2 and 3. The model describes health states that individuals can enter. Predictors describe the likelihood of these and subsequent events occurring at various, often continuous, time points (represented as time-to-event). Costs and quality of life weights are to be attached to events and time spent in different health conditions to estimate long-term costs and health outcomes.[17]

The model starts with the valve implantation. Patients can survive the intervention or not. When patients survive the intervention, they can remain 'alive', die from non-valve related causes or experience a valve-related event. Patients experiencing an event can die without receiving treatment or receive treatment for the event. After treatment patients can die or survive the event. When patients survive the event, they can stay alive, experience another event or die due to non-valve related causes. The quality of life and costs of being alive after an event depend on the experienced event. The transition probabilities of patients moving from one health condition to another depend on predictors.

Figure 3 provides a detailed explication of the same CM as presented in Figure 2. In Figure 3 the valve-related events and treatment options are specified and the events are divided into early (<30 days after the intervention) and late events. The definitions of these events are based on clinical outcome reporting guidelines.[18, 19] Some events are more common in patients undergoing transcatheter valve implantation than surgical valve replacement and vice versa. However, to be able to compare interventions all events are to be included for every intervention.

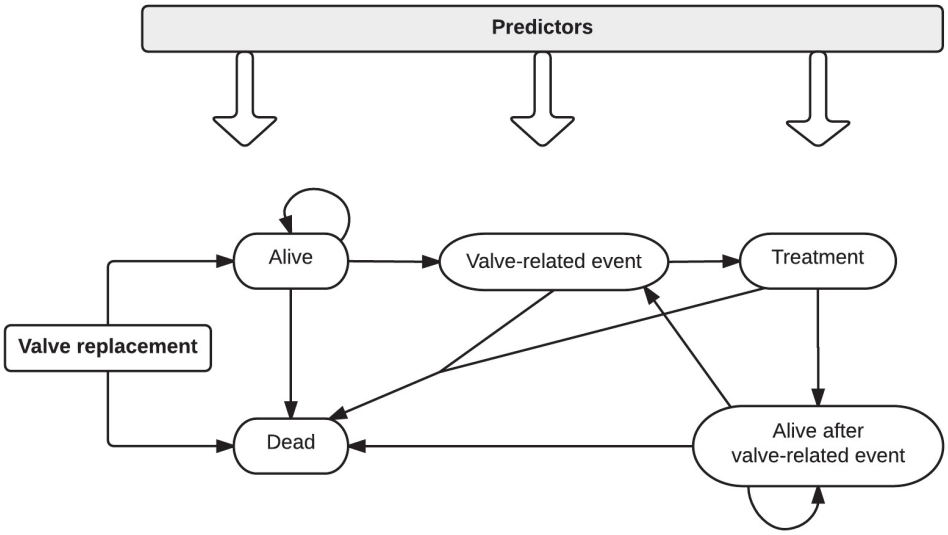


Figure 2. Draft simple conceptual model for the early health technology assessment of tissue-engineered heart valves.

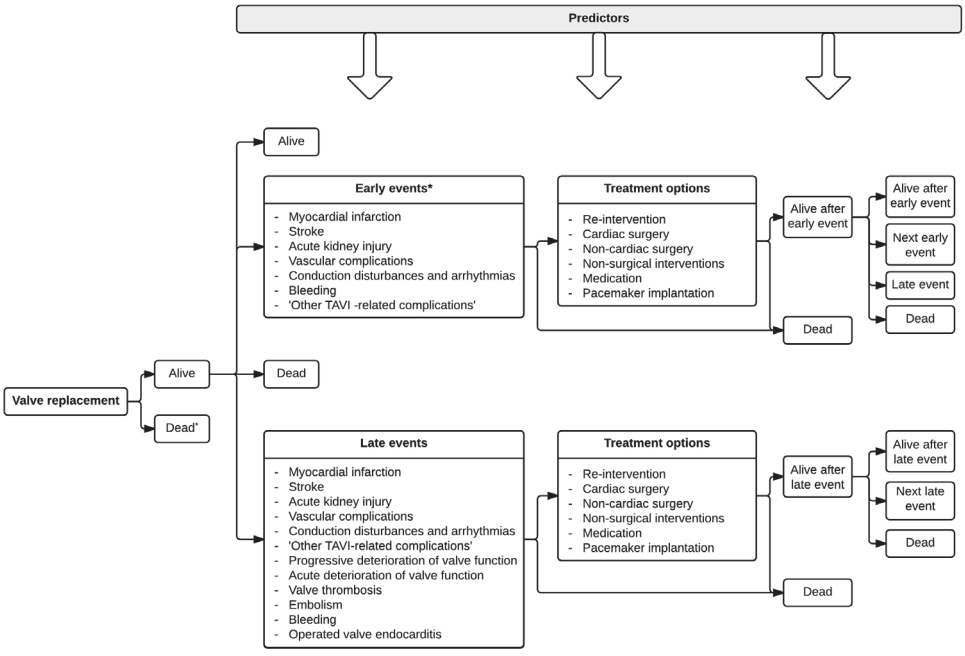


Figure 3. Draft detailed conceptual model for the early health technology assessment of current and novel heart valve interventions. *within 30 days after the intervention.

Literature review

The systematic literature review identified 14 studies reporting decision-analytic models for economic evaluation of heart valve implantations.[20-33] The following elements in the structures of existing models were remarkable and were discussed with the experts to determine whether and how these elements should be operationalized in our model. First, in the existing models, the events are not as detailed as in our model; when complications are included, several valve-related events are combined or less valve-related events are included. Second, the events that are included in the short-term or long-term differ between studies. Third, conversion to surgical aortic valve replacement is sometimes included as option in models considering TAVI.

Expert opinion

The input from the first two experts resulted in an updated model illustrated in Figure S1. Subsequently, we recruited eight additional experts resulting in a Delphi panel with 10 panellists. The updated CM was discussed with seven of the eight panellists during semistructured interviews. After the interviews, two rounds of online questionnaires were send out to all 10 panellists. The first questionnaire was answered by eight panellists and the second questionnaire by 10 panellists. The results of the input from the first two experts and the Delphi panel are described in detail in the Supplementary Material. The following describes the most important changes that were made based on the expert's opinions to obtain the final CM (Figure 4).

- The events are separated into cardiovascular, non-cardiovascular and prosthetic valve-related events to obtain a logic model structure. All events in the model are related to the heart valve intervention, but the events in the category 'prosthetic valve-related events' are directly related to the heart valve substitute.
- The following events are considered only during the first 30 days after the intervention because after that period the events are not necessarily related to the intervention: myocardial infarction, vascular complications, atrial fibrillation, pacemaker implantation and acute kidney injury. The other events are to be considered during the rest of the patient's lifetime using time-to-event rates.
- The event 'stroke' is redefined as 'cerebrovascular accident' to include both strokes and transient ischemic attacks.
- Except for atrial fibrillation during the first 30 days after the intervention, conduction disturbances and arrhythmias are only included in the model when they result in pacemaker implantation. Otherwise these events were considered less relevant.
- The distinction between acute and progressive deterioration of valve function was found to be unrealistic because the (changes in) the rate of deterioration can often not be established in clinical practice. Therefore, these events are combined

into one event called 'prosthetic valve dysfunction', including structural valve deterioration, non-structural valve dysfunction and valve malpositioning.

- Instead of the general term 'embolism' two severe consequences of embolism – stroke and myocardial infarction – are included in the model to avoid double counting of events.
- Conversions from transcatheter valve implantation to open surgery and vice versa are added to the model.
- The group of events 'Other TAVI-related complications' is excluded from the model as a separate category. Instead, these events are included in other categories of events or excluded (see Supplementary Material for more details).

In addition to inclusion of events in the CM, the typical treatment strategies for the events were discussed with the Delphi panellists. Based on their advice, we included the most common treatment options presented in Table 1.

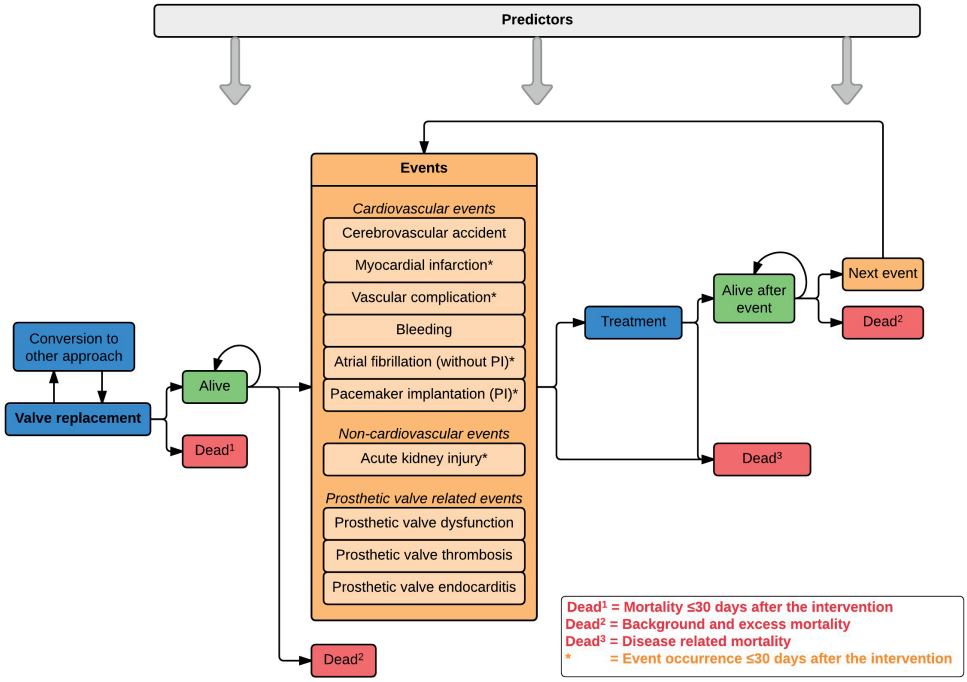


Figure 4. Final conceptual model for the early health technology assessment of current and novel heart valve interventions.

Cerebrovascular accident includes strokes and transient ischemic attacks. Prosthetic valve dysfunction includes structural valve deterioration (SVD), non-structural valve dysfunction (NSVD) and valve-malpositioning. Treatment includes the typical treatment strategies for the events in the model (Table 1). Background and excess mortality: Some of the non-valve related mortality will be comparable with mortality in the general population (background mortality). The remaining non-valve related mortality can be ascribed to the excess risk of dying of patients that underwent heart valve interventions (excess mortality). The excess mortality can be explained by increased occurrence of sudden death, underreporting of valve-related events, and underlying pathology such as left ventricular hypertrophy.

Table 1. Typical treatment strategies of events included in the conceptual model.

Cardiovascular events	
Cerebrovascular accident	Conservative management (antiplatelets and/or anticoagulants and watchful waiting)
	Thrombolysis (in-hospital)
	Mechanical thrombectomy
Myocardial infarction	Conservative management
	Percutaneous coronary intervention (PCI)
	Coronary artery bypass grafting (CABG)
Vascular complication	Conservative management (in-hospital monitoring with duplex sonography)
	Endovascular stent or balloon therapy
	Surgical repair
Bleeding	Optimization of anticoagulation control
	Blood transfusion
	Surgical repair of bleeding location
	Re-intervention*
Atrial fibrillation (without PI)	Medication (anticoagulants)
	Electric cardioversion
Conduction disturbances and arrhythmias	Pacemaker implantation (PI)‡
Non-cardiovascular events	
Acute kidney injury	Conservative management (diuretics to correct volume overload)
	Continuous veno-venous hemofiltration (CVVH)
	Chronic dialysis
	Kidney transplant
Prosthetic valve related events	
Prosthetic valve dysfunction	Conservative management (heart failure medication and watchful waiting)
	Re-intervention*
Prosthetic valve thrombosis	Thrombolysis (in-hospital)
	Re-intervention: valve replacement
Prosthetic valve endocarditis	Antibiotic treatment (in-hospital)
	Re-intervention: valve replacement

*Re-intervention can be surgical repair or replacement/valve-in-valve implantation of another valve substitute
‡Patients with conduction disturbances and arrhythmias other than atrial fibrillation without the need for pacemaker implantation are excluded.

DISCUSSION

This study provided a CM to perform early HTA of tissue-engineered heart valves expected to be used in clinical practice in the future. By using a comprehensive approach, including a systematic literature review and input from a Delphi panel with experts, the CM developed in this study has become a valuable representation of the most important consequences after heart valve interventions.

The CM serves as the foundation of the decision-analytic model that will be used to perform early HTA of tissue-engineered heart valves. Although the model is developed for tissue-engineered heart valves, it can also be applied to estimate the cost-effectiveness of currently used heart valve interventions and other novel heart valve interventions such as minimally invasive valve surgery and robotically assisted valve surgery.

Before we can perform cost-effectiveness analyses with our decision-analytic model, data need to be collected on the input parameters of the model. Three types of input parameters can be distinguished: (1) time spent in health states and transition probabilities (chance of moving from one health state to another), (2) quality of life weights and (3) societal costs of patients, in every health state in the CM. In early HTA, the interventions under study are not used in clinical practice yet. Therefore, we will need to make assumptions about the input parameters for tissue-engineered heart valves. These assumptions will be based on the results of animal studies and expert opinion of biomedical scientists developing tissue-engineered heart valves and clinicians. The accompanying uncertainty of these assumptions will be analysed using exploratory sensitivity and scenario analyses. In contrast to tissue-engineered heart valves, the input parameters for the current standard of care can be based on real-world evidence. Time spent in health states and transition probabilities will be based on clincial data registries and systematic reviews and meta-analyses.[34] Healthcare costs are currently being estimated using claims data from health insurers. Quality of life and costs outside of healthcare (i.e. productivity and informal care costs) are collected using patient-reported questionnaires.

Once the input parameters are collected, we can use our decision-analytic model to perform the following analyses. First, the cost-effectiveness of currently used heart valve substitutes can be determined. Second, a benchmark can be set for the minimum performance requirements and maximum costs of tissue-engineered heart valves to be cost-effective compared to currently used heart valve substitutes. If it is not likely that the performance requirements will be met or when the costs of the new intervention appear to be too high compared to currently used heart valve substitutes, continuing

investment in tissue-engineered heart valves may not be worthwile. Third, when it seems feasible to meet the performance requirements and implant tissue-engineered heart valves under the maximum allowed costs to be cost-effective, more detailed cost-effectiveness analyses can be performed by simulating various scenarios with the decision-analytic model. In these scenarios the impact of different assumptions on the performance and costs on the cost-effectiveness of tissue-engineered heart valves can be simulated. These scenario analyses can be modified and repeated as more information becomes available during the development process of tissue-engineered heart valves. Fourth, we can also use our decision-analytic model to determine the probabilities and size of return on investments of developers of tissue-engineered heart valves. The potential revenue can be calculated by multiplying the difference in the proposed sales price and expected production costs of tissue-engineered heart valves with the expected number of patients per year.[35] Relevant scenarios with different estimates of the sales price, production costs, number of patients per year and speed of adoption of the novel heart valve intervention can be simulated. Finally, a budget impact analysis can be performed to address the expected changes in the expenditure of the national health care system after the adoption of the new heart valve intervention. These analyses can inform health care decision makers and health insurers about potential financial consequences.

The results of early HTA can be useful for different stakeholders. First, it provides guidance to developers of tissue-engineered heart valves in further development of the technology, setting realistic performance-price goals, and designing and managing reimbursement strategies.[36] Second, it informs clinicans about future treatment options which may result in faster adoption of tissue-engineered heart valves in clinical practice.[37] Finally, healthcare payers are informed earlier about potential interventions that may enter the market in the future, which may result in more timely decisions about reimbursement.[37]

Despite the potentials of (early) HTA, there are also limitations. First, all models represent a simplification of reality. Therefore, decisions had to be made about what is relevant to include. This study enables readers to gain insight in the choices that were made and the reasons for making simplifying assumptions when necessary. Second, there were some events for which consensus could not be reached within the Delphi panel: including transient ischemic attacks in addition to stroke, excluding or including atrial fibrillation during the first 30 days after the intervention, and including myocardial infarction and pacemaker implantation during the first 30 days after the intervention instead of over the patient's lifetime. In these cases, the small workgroup (SH, MR, JT) decided about the inclusion of these events. However, these decisions may alter the results of the model.[9] In case sufficient data is available, we can perform sensitivity

analysis for these events to determine their influence on the outcomes. Third, although most panellists initially did not agree, we had to decide to model the various types of prosthetic v alve dysfunction in the same way because it is not feasible to incorporate different rates of deterioration of quality of life because of limited data availability. However, the majority of the panellists did not object to this decision in the final questionnaire.

CONCLUSIONS

The future promises many emerging technologies in the field of heart valve interventions. Prior to implementation in clinical practice it is essential to perform early HTA to inform stakeholders about the potential return on investment and societal impact of the new technology. In this study, we developed a CM that will be used as the foundation of a decision-analytic model that can estimate the cost-effectiveness of current heart valve interventions and the potential cost-effectiveness of novel heart valve interventions in the early development stages, especially tissue-engineered heart valves. The results of this early HTA will especially be useful for the developers of tissue-engineered heart valves because it can guide them in further development of the interventions. However, it also helps clinicians and healthcare payers in identifying promising applications of tissue-engineered heart valves, which may results in faster take-up in clinical practice and reimbursement by healthcare payers.

Funding. The authors acknowledge the support from the Netherlands Cardio Vascular Research Initiative: The Dutch Heart Foundation, Dutch Federation of University Medical Centers, the Netherlands Organization for Health Research and Development and the Royal Netherlands Academy of Sciences.

Conflicts of interest. None.

REFERENCES

1. Nkomo VT et al. *Burden of valvular heart diseases: a population-based study.* The Lancet 2006;368(9540):1005-11
2. Vahanian A, Alfieri O, Andreotti F, et al. *Guidelines on the management of valvular heart disease (version 2012) The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS).* Eur. Heart J. 2012;**33**(19):2451-96
3. Bouten CVC, Driessen-Mol A, Baaijens FPT. *In situ heart valve tissue engineering: simple devices, smart materials, complex knowledge.* Expert Review of Medical Devices 2012;**9**(5):453-55
4. Mol A et al. *Tissue engineering of heart valves: advances and current challenges.* Expert Review of Medical Devices 2009;**6**(3):259-75
5. de Meijer C et al. *The effect of population aging on health expenditure growth: a critical review.* European Journal of Ageing 2013;**10**(4):353-61
6. Siebert U. *When should decision-analytic modeling be used in the economic evaluation of health care?* Eur J Health Econom 2003;**3**:143
7. Ijzerman MJ, Steuten LMG. *Early assessment of medical technologies to inform product development and market access.* Applied health economics and health policy 2011;**9**(5):331-47
8. Markiewicz K, van Til JA, Ijzerman MJ. *Medical devices early assessment methods: Systematic literature review.* Int. J. Technol. Assess. Health Care 2014;**30**(02):137-46
9. Roberts M et al. *Conceptualizing a model a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–2.* Med. Decis. Making 2012;**32**(5):678-89
10. Rosenhek R et al. *ESC Working Group on Valvular Heart Disease Position Paper: assessing the risk of interventions in patients with valvular heart disease.* Eur. Heart J. 2012;**33**(7):822-28
11. Nishimura RA et al. *2014 AHA/ACC guideline for the management of patients with valvular heart disease.* J. Am. Coll. Cardiol. 2014;**63**(22):2438–88
12. Hsu C-C, Sandford BA. *The Delphi technique: making sense of consensus. Practical Assessment*, Research & Evaluation 2007;**12**(10):1-8
13. Takkenberg JJM et al. *The Ross procedure a systematic review and meta-analysis.* Circulation 2009;**119**(2):222-28
14. Ghawi H, Kenny D, Hijazi ZM. *Transcatheter pulmonary valve replacement.* Cardiology and Therapy 2012;**1**(1):1-14
15. Genereux P et al. *Transcatheter aortic valve implantation 10-year anniversary: review of current evidence and clinical implications.* Eur. Heart J. 2012;**33**(19):2388-+ doi: DOI 10.1093/eurheartj/ehs220[published Online First: Epub Date]|.
16. Rutten-van Mölken MPMH, Groot CA, Al MJ. *Van kosten tot effecten: een handleiding voor economische evaluatiestudies in de gezondheidszorg*: Elsevier Gezondheidszorg, 2010.
17. Karnon J et al. *Modeling Using Discrete Event Simulation A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force–4.* Med. Decis. Making 2012;**32**(5):701-11

18. Akins CW et al. Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions. Eur. J. Cardiothorac. Surg. 2008;**33**(4):523-28
19. Kappetein AP et al. *Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 Consensus Document†*. J. Am. Coll. Cardiol. 2012;**60**(15):1438-54
20. Beresniak A et al. *Cost-effectiveness of mitral valve repair versus replacement by biologic or mechanical prosthesis.* Ann. Thorac. Surg. 2013;**95**(1):98-104 doi: 10.1016/j.athoracsur.2012.08.005
21. Brecker S et al. *Cost-utility of transcatheter aortic valve implantation for inoperable patients with severe aortic stenosis treated by medical management: a UK cost-utility analysis based on patient-level data from the ADVANCE study.* Open heart 2014;**1**(1):e000155
22. Doble B et al. *Cost-effectiveness of the Edwards SAPIEN transcatheter heart valve compared with standard management and surgical aortic valve replacement in patients with severe symptomatic aortic stenosis: A Canadian perspective.* The Journal of Thoracic and Cardiovascular Surgery 2013;**146**(1):52-60. e3
23. Fairbairn TA et al. *The cost-effectiveness of transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis at high operative risk.* Heart 2013;**99**(13):914-20 doi: 10.1136/heartjnl-2013-303722
24. Gada H et al. *Markov model for selection of aortic valve replacement versus transcatheter aortic valve implantation (without replacement) in high-risk patients.* The American Journal of Cardiology 2012;**109**(9):1326-33
25. Gada H, Agarwal S, Marwick TH. *Perspective on the cost-effectiveness of transapical aortic valve implantation in high-risk patients: Outcomes of a decision-analytic model.* Annals of Cardiothoracic Surgery 2012;**1**(2):145-55
26. Hancock-Howard RL et al. *Cost effectiveness of transcatheter aortic valve replacement compared to medical management in inoperable patients with severe aortic stenosis: Canadian analysis based on the PARTNER Trial Cohort B findings.* Journal of Medical Economics 2013;**16**(4):566-74
27. Murphy A, et al. *Transcatheter aortic valve implantation for severe aortic stenosis: the cost-effectiveness case for inoperable patients in the United Kingdom.* Int. J. Technol. Assess. Health Care 2013;**29**(01):12-19
28. Neyt M et al. *A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population.* BMJ open 2012;**2**(3)
29. Orlando R et al. *Cost-effectiveness of transcatheter aortic valve implantation (TAVI) for aortic stenosis in patients who are high risk or contraindicated for surgery: A model-based economic evaluation.* Health Technol. Assess. 2013;**17**(33):1-86 doi: 10.3310/hta17330
30. Queiroga MACQ, et al. *Transcatheter aortic valve implantation for the treatment of severe aortic valve stenosis in inoperable patients under the Perspective of the Brazilian Supplemental health system - Cost-effectiveness analysis.* Rev Bras Cardiologia Invasia 2013;**21**(3)
31. Report to Scottish Health Technologies Group (SHTG). *Evidence Development Pilot Project:Transcatheter Aortic Valve Implantation in Scotland*, 2010.

32. Simons CT et al. *Transcatheter Aortic Valve Replacement in Nonsurgical Candidates With Severe, Symptomatic Aortic Stenosis A Cost-Effectiveness Analysis.* Circulation: Cardiovascular Quality and Outcomes 2013;**6**(4):419-28
33. Watt M et al. *Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement.* Heart 2012;**98**(5):370-76 doi: 10.1136/heartjnl-2011-300444[published Online First: Epub Date]|.
34. Huygens SA et al. *Contemporary outcomes after surgical aortic valve replacement with bioprostheses and allografts: a systematic review and meta-analysis.* Eur. J. Cardiothorac. Surg. 2016:ezw101
35. Cosh E et al. *Investing in new medical technologies: A decision framework.* Journal of Commercial Biotechnology 2007;**13**(4):263-71
36. Pietzsch JB, Paté-Cornell ME. *Early technology assessment of new medical devices.* Int. J. Technol. Assess. Health Care 2008;**24**(01):36-44
37. Buisman LR et al. *The early bird catches the worm: Early cost-effectiveness analysis of new medical tests.* Int. J. Technol. Assess. Health Care 2016:1-8

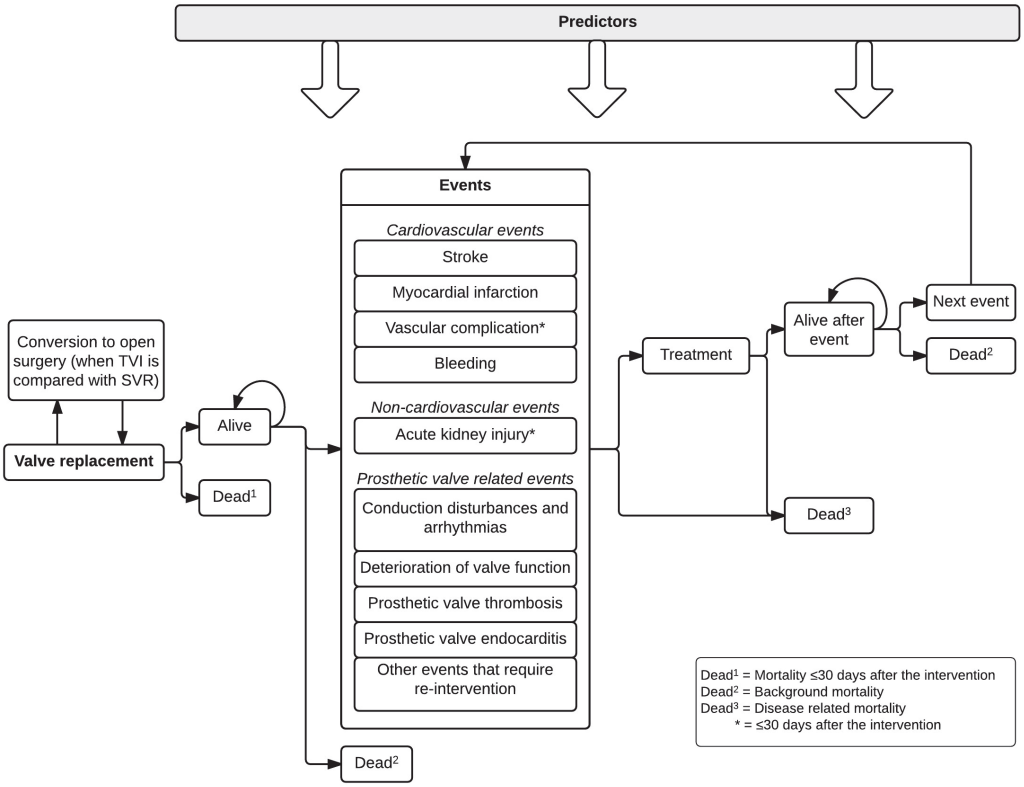


Figure S1. Draft conceptual model for the early health technology assessment of tissue-engineered heart valves as shown to the Delphi panel.

SUPPLEMENTARY MATERIAL

Results of first input from experts and Delphi panel

First input from two clinical experts

After the discussion of the conceptual model with the clinical experts we re-evaluated the draft conceptual model (Figure S1). The following describes the most important changes that were made to obtain the new conceptual model.

First, the events are separated into cardiovascular events, non-cardiovascular events and prosthetic valve associated events to obtain a logic model structure.

Second, embolism is excluded from the model to avoid double counting of events. Instead two severe consequences of an embolism – stroke and myocardial infarction – are included.

Third, the experts agreed that the distinction between acute and progressive deterioration of the valve function was unrealistic and is not reflected in clinical guidelines. Therefore these events are combined into one event called: deterioration of valve function.

Fourth, the experts stated that events should not be divided in early and late events; instead timing of the events should be based on time-to-event rates. However, acute kidney injury and vascular complications are events that only occur as a consequence of the intervention within the first 30 days after the intervention. Therefore these events will only be included on the short-term as a discrete variable: the complication occurred within 30 days after the intervention or not. Time-to-event rates will be estimated for all other events.

Finally, the experts did not agree about the inclusion of the 'other TAVI-related complications' defined in the Valve Academic Research Consortium (VARC) guidelines. (24, 26) One panellist felt that these are technical complications that are not as relevant for the patient's quality of life compared to clinical complications, while the other panellist felt that these complications should be included in the model.

In the new model these complications will only be included when they require re-intervention. The inclusion of these events was further discussed with the experts in the Delphi panel. The first input from the two experts resulted in the model illustrated in Figure S1.

Delphi panel

The results of the interviews, first and second online questionnaire answered by the Delphi panel are described in detail per event in this appendix.

1. Cardiovascular events

1.1 Cerebrovascular accidents (CVA)

Interviews

In the draft conceptual model shown to the panellists only strokes were included. During the interviews several panellists suggested the inclusion of transient ischemic attacks (TIAs). Therefore this question was included in the first questionnaire to the panellists.

Questionnaire 1

Three panellists felt that TIAs should not be included in the model because it is hard to determine whether a patient suffered from a TIA and it does not have lasting consequences for the patient. In contrast, five panellists argued that TIAs should be included in the model because it is hard to distinguish TIAs from strokes. There was no consensus, but the majority of the panellists wanted to include TIAs in the model. Therefore it was decided to include TIAs in the conceptual model for now. When it appears to be unfeasible to collect data about TIAs in addition to strokes, this decision can be reassessed. The event 'stroke' is now called 'cerebrovascular accident (CVA)', including both strokes and TIAs.

Questionnaire 2

In the second questionnaire eight panellists did not have objections to this choice. Two panellists still felt that TIAs should not be included in the model because it is hard to determine whether a patient suffered from a TIA and the impact on quality of life is limited. Furthermore, large trials do not included TIA as an outcome. Since the majority of the Delphi panel is in favor of including TIAs, TIAs will be included in the base model.

1.2 Myocardial infarction

Interviews

During the interviews several panellists doubted whether a myocardial infarction can be considered as consequence of the heart valve intervention when they occur long after the intervention took place. In the questionnaire the panellists were asked whether myocardial infarction should be considered over a lifelong time horizon or only in a short post-procedure period.

Questionnaire 1

None of the panellists thought it was important to include myocardial infarction during the patient's lifetime. There was no consensus about the time period to take into account myocardial infarctions: within 72 hours or 30 days after the intervention.

Therefore it was decided to include myocardial infarctions during the first 30 days after the intervention.

Questionnaire 2

In de second questionnaire nine panellists did not have objections to this choice. However, one (new) panellist would like to incorporate myocardial infarction longer than 30 days, preferably during the patients' lifetime. According to this panellist it is possible there will be differences in the occurrence of myocardial infarction between surgical valve replacement and transcatheter valve implantation. One other panellist agreed to include myocardial infarction only on the short term, but suggested to include myocardial infarction during the first three months because of the use of oral anticoagulants (for example with bioprostheses). However, lifetime myocardial infarctions are not included in the base model since the majority of the panellists advised to exclude myocardial infarctions after the first 30 days after the intervention.

1.3 Vascular complications

Vascular complications are events that only occur as a consequence of transcatheter valve implantation within the first 30 days after the intervention. Therefore this event will only be included on the short term as a discrete variable: the complication occurred within 30 days after the intervention or not. None of the panellists objected to this decision.

1.4 Bleeding

The event 'bleeding' includes postoperative bleedings (cardiac tamponades) and anti-coagulant related bleedings and will be considered over the patients' lifetime. None of the panellists had comments about this event.

1.5 Atrial fibrillation

Interviews

In the draft conceptual model all types of conduction disturbances and arrhythmias were included. During the interviews the panellists were asked whether they felt it was important to take into account all the types of conduction disturbances and arrhythmias. The majority of the panellists agreed that atrial fibrillation (AF) should be included in the model as a separate event because it is a common complication after heart valve intervention in the postintervention phase.

Questionnaire 1

Although atrial fibrillation is a common complication after heart valve intervention in the postintervention phase, on the long term atrial fibrillation is a common complication in the general elderly population (with or without valve problems) due

to aging. Therefore the panellists were asked during what time period they thought atrial fibrillation should be included in the model.
Five panellists agreed to only include atrial fibrillation during the first 30 days after the intervention. The other three panellists did not agree but it was unclear whether they would include atrial fibrillation during the patient's lifetime or not at all. Therefore this question was included in the second questionnaire. Furthermore, we asked the panellists whether we should include both transient and persistent atrial fibrillation (>7 days according to the ESC guideline 2010) or only persistent atrial fibrillation.

Questionnaire 2
In the second questionnaire two panellists did not have an opinion about the inclusion of atrial fibrillation in the model. Six panellists would like to include both transient and persistent atrial fibrillation, but only during the first 30 days to ensure there is a relationship between the intervention and occurrence of atrial fibrillation. One panellists agreed to include atrial fibrillation only during the first 30 days, but only persistent atrial fibrillation. In addition, this panellist argued that atrial fibrillation should not be arrayed under prosthetic valve events. Finally, one panellist argued that atrial fibrillation should not be included in the model at all because many patients experience transient atrial fibrillation within the first 30 days and most of these patients do not experience severe consequences, neither in terms of subsequent consequences nor reduced quality of life. The majority of the panellists chose to include atrial fibrillation (both transient and persistent) during the first 30 days. Therefore atrial fibrillation that occurs more than 30 days after the intervention will not be included in the model.

1.6 Pacemaker implantation
Interviews
The other types of conduction disturbances and arrhythmias were considered less relevant. However, one major consequence of these conduction disturbances and arrhythmias can be the implantation of a pacemaker. Therefore the panellists were asked if all other conduction disturbances and arrhythmias (besides AF) should be included in the model or only when it results in pacemaker implantation.

Questionnaire 1
All panellists agreed that it is sufficient to include conduction disturbances and arrhythmias only when they result in pacemaker implantation (PI). Therefore (with the exception of atrial fibrillation during the first 30 days after the intervention) conduction disturbances and arrhythmias without the need for pacemaker implantation will not be included in the model.

Questionnaire 2

In the second questionnaire the panellists were asked over what time period pacemaker implantation should be considered. There was no consensus about this subject in the Delphi panel. One panellist did not have an opinion. Six panellists agreed to include pacemaker implantation only during the first 30 days after the intervention because during that time period there is more certainty that the need for pacemaker implantation is a consequence of the intervention. However, three panellists felt pacemaker implantation should be included during the patient's lifetime. Therefore it was decided to include pacemaker implantation during the first 30 days after the intervention in the base model.

2. Non-cardiovascular events

2.1 Acute kidney injury

Acute kidney injury only occurs as a consequence of the heart valve intervention within the first 30 days after the intervention. Therefore this event will only be included on the short term as a discrete variable: the complication occurred within 30 days after the intervention or not. None of the panellists objected to this decision during the interviews.

3. Prosthetic valve related events

3.1 Prosthetic valve dysfunction

Interviews

In the draft conceptual model structural valve deterioration (SVD) and non-structural valve dysfunction (NSVD) were combined in the event 'deterioration of valve function'. Some of the panellists noted that after transcatheter valve implantation it is possible that the prosthetic valve does not function well from the beginning. The name 'deterioration of valve function' does not reflect this event. Therefore the name of this event was changed to 'prosthetic valve dysfunction'.

Questionnaire 1

In the questionnaire the panellists were asked whether the consequences in terms of treatment and quality of life of the events included in 'prosthetic valve dysfunction' can be considered comparable. Most panellists agreed that treatment of different types of prosthetic valve dysfunction is comparable; in most cases re-intervention. However, they felt that there are differences in the timing of re-intervention and the deterioration quality of life of patients with SVD (slowly deteriorating quality of life and need for re-intervention) or NSVD (more rapidly deterioration in quality of life and need for re-intervention). However it is not feasible to incorporate the speed of deterioration of

quality of life in the model because of limited available data. Therefore it was decided to model the different types of prosthetic valve dysfunction in the same way.

Questionnaire 2
In the second questionnaire nine panellists did not have objections to this choice. However, one (new) panellist felt that the consequences of these events are not comparable. It was decided to model the different types of prosthetic valve dysfunction in the same way because the majority of the panellists agreed with this decision.

3.2 Prosthetic valve thrombosis and endocarditis
Interviews
The panellists did not have remarks about these events. Both prosthetic valve thrombosis and endocarditis will be considered over the patients' lifetime.

3.3 Other TAVI-related complications in the VARC-2 guideline
Interviews
In the "Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation: the Valve Academic Research Consortium-2 Consensus Document"(26) several 'other TAVI-related complications' are defined in addition to the events described above: conversion to open surgery, unplanned use of cardiopulmonary bypass, coronary obstruction, ventricular septal perforation, mitral valve apparatus damage or dysfunction, cardiac tamponade, endocarditis, valve thrombosis, valve malpositioning, valve embolization, TAV-in-TAV deployment. The occurrence of these complications is relatively low.(33) Therefore the importance of including these events in the model was discussed with the panellists. Endocarditis and valve thrombosis are already included in the model and are therefore not discussed in this paragraph.

3.3.1 Conversion to open surgery and unplanned use of cardiopulmonary bypass
Interviews
According to the panellists the event 'conversion to open surgery' overlaps with 'unplanned use of cardiopulmonary bypass.' Therefore these events will be combined to one event. Some panellists suggested that if we include 'conversion to open surgery' in the model, the flipside of this event (conversion to transcatheter valve implantation) should also be added to the model. This suggestion was added as a question to the questionnaire.

Questionnaire 1
Most panellists agreed that conversions from one approach to the other are important complications. Two panellists felt that both conversions were not important to take into account. One of these panellists argued that conversion from transcatheter

valve implantation to open surgery is fatal for most patients. However, because these conversions are accompanied with significant costs it was decided to include them in the model (on the condition that relevant data is available or can be collected).

Questionnaire 2
In the second questionnaire none of the panellists had objections to this decision.

3.3.2 Coronary obstruction

Interviews
During the interviews some panellists argued that in most cases coronary obstruction results in a myocardial infarction or death. That means that those patients are already included in the model. Therefore the other panellists were asked in the questionnaire whether it is reasonable to exclude coronary obstruction as a separate event from the model.

Questionnaire 1
Five panellists agreed that coronary obstruction should not be included in the model because the most common consequences of coronary obstruction (i.e. myocardial infarction and death) are already included in the model. Three panellists felt that coronary obstruction should be included in the model. One of these panellists felt this way because coronary obstruction can lead to conversion to open surgery. However, in these cases the event will also be included in the 'conversion to open surgery' event. The other two panellists argued that coronary obstruction does not have to result in myocardial infarction or death when it is discovered in time. Despite these arguments it was decided to exclude coronary obstruction from the model to prevent overlap with MI. Furthermore, the occurrence rate of coronary obstruction after TAVI is relatively low (i.e. pooled estimate rate of 0.7% in meta-analysis of Genereux et al. 2012(33)).

Questionnaire 2
The panellists do not have objections to this decision. However, one panellist would like to know the percentage of myocardial infarctions caused by coronary obstruction.

3.3.3 Ventricular septal perforation and mitral valve apparatus damage or dysfunction

Interviews
Ventricular septal perforation and mitral valve apparatus damage or dysfunction are major complications that occur relatively rarely after heart valve interventions. The panellists did not reveal a clear opinion about the inclusion of these events in the model. Therefore the questions were added to the questionnaire.

Questionnaire 1

The panellists did not agree about the inclusion of ventricular septal perforation and mitral valve apparatus damage or dysfunction in the model. These events were considered for inclusion in the model because the VARC guideline discussed them under 'other TAVI-related events'. The events are not defined in the Guideline for reporting events after cardiac valve interventions(23) (mostly used for surgical valve replacement) and therefore seem less relevant after surgical valve replacement. The intervention cardiologists in the Delphi panel that performed TAVI regularly agreed that these complications were not relevant for the model because of their low occurrence rate. Furthermore, there is limited data available about the occurrence of these complications after transcatheter valve implantation or surgical valve replacement. To assure that we focus on the most relevant complications and to limit the model's complexity, it was decided to follow the intervention cardiologists' opinion and exclude ventricular septal perforation and mitral valve apparatus damage or dysfunction from the model.

Questionnaire 2

Seven panellists do not have objections to this choice. One panellist did not have an opinion. However, two panellists objected to the exclusion of these events. One of these panellists argued that these complications almost always occur after transcatheter valve implantation and not after surgical valve replacement and is therefore an important difference between these types of interventions. The other panellist felt that excluding these events because of their rarity is not a valid reason. However, it was decided to exclude these events from the model, because the majority of the panellists agree with this decision and data about these events is limited.

3.3.4 Cardiac tamponade

According to the panellists cardiac tamponade could be included in the (postintervention) bleeding event.

3.3.5 Valve malpositioning

As described before the definition of 'deterioration of valve function' was changed to 'prosthetic valve dysfunction'. Therefore valve malpositioning can be included in this event.

3.3.6 Valve embolization

As described in the paper, embolism is excluded from the model as a separate event, because two severe consequences of an embolism (stroke and MI) are already included in the model. Including both the underlying mechanism and the resulting complications would lead to double counting of the events. However, because of this

change in the model an embolism that not results in a stroke or myocardial infarction – like other noncerebral embolic events – are not included in the model.

3.3.7 TAV-in-TAV deployment

TAV-in-TAV deployment (valve-in-valve implantation) can occur during or after the index procedure. If an additional valve needs to be included during the index procedure, this will be incorporated in the index procedure itself (by adding costs to the proportion of the valve implantations where a second valve is implanted). When valve-in-valve implantation occurs after the index procedure, it will be included as a treatment option. Therefore this complication will not be included as a separate event in the conceptual model.

4. Additional events

After discussing the draft conceptual model, the Delphi panellists were asked if the draft conceptual model was complete or additional events needed to be added. Several panellists suggested additional events. The suggested events were considered within the small workgroup (SH, MR, JT). Three of the suggested events were not added to the model. (1) Respiratory and urinary tract infections were not included, because they are not specific to heart valve interventions. (2) Rheumatic fever is a potential event in developing countries. However, our conceptual model is based on the Dutch healthcare system and data from developed countries. Therefore rheumatic fever will not be added to the conceptual model. (3) Patients with less than optimal quality of life without experiencing any of the events included in the model will not be added explicitly in the conceptual model. The quality of life of these patients will be reflected in the average quality of life of patients that are alive after the intervention without experiencing any events included in the model. The other two suggested events (heart failure and post-surgery neurological problems) were included in the questionnaire for consideration by the other panellists.

4.1 Heart failure

Questionnaire 1

Five panellists argued that heart failure should not be included in the model when there is no association with the valve substitute. One of these panellists suggested incorporating cardiac hospital admissions instead. Three panellists felt that heart failure should be taken into account when it results in hospitalization of the patient.
It was decided that heart failure will not be incorporated as an event in the model, because heart failure that is not caused by valve problems is not relevant for our decision problem. It is assumed that heart failure that is caused by valve problems is included in the model in the hospitalizations due to prosthetic valve dysfunction.

Questionnaire 2
In the second questionnaire none of the panellists had objections to this decision.

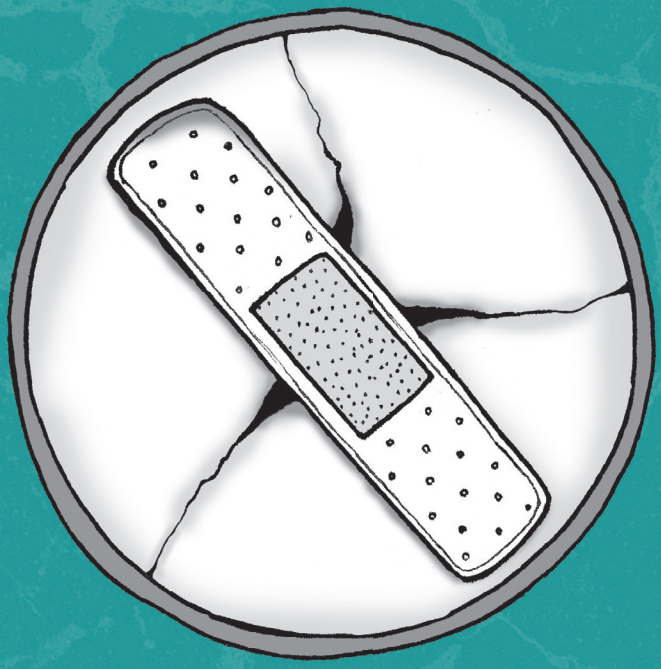
4.2 Post-narcotic problems and delirium
Questionnaire 1
All panellists agreed it is not feasible to include post-narcotic problems and delirium in the model, because there is limited data available about the occurrence, impact on quality of life and costs of these events.

5. Summary

In summary, the input from the Delphi panel resulted in the following changes in the model.

- In addition to conversion from transcatheter valve implantation to open surgery, conversion from surgical valve replacement to transcatheter valve implantation is included in the model.
- Transient ischemic attacks (TIA) are added to the model. The event 'stroke' is redefined as 'cerebrovascular accident' and includes both strokes and TIAs.
- Myocardial infarction (MI) is only included during the first 30 days after the intervention and not during the patient's lifetime, because the majority of the panellists felt that myocardial infarctions that occur on the long term generally are not a direct consequence of the heart valve intervention.
- Except for atrial fibrillation (AF) during the first 30 days after the intervention, conduction disturbances and arrhythmias are excluded from the model, unless they result in pacemaker implantation (PI).
- Atrial fibrillation is only included during the first 30 days after the intervention instead of during the patient's lifetime because the majority of the panellists agreed that the occurrence of atrial fibrillation beyond the first postinterventional month is not necessarily a direct consequence of the heart valve intervention, but a common complication in the elderly population (with or without valve problems) due to aging..
- Atrial fibrillation (without pacemaker implantation) and pacemaker implantation are included in the category of cardiovascular events instead of prosthetic valve related events.
- Deterioration of valve function is now called prosthetic valve dysfunction including structural valve deterioration (SVD) and non-structural valve dysfunction (NSVD).
- 'Other events that require re-intervention' are excluded from the model. The following describes which events are included or excluded.
  - Conversion to open surgery is included separately.
  - Cardiac tamponade is included in 'bleeding'.

- Valve malpositioning is included in 'prosthetic valve dysfunction'.
- TAV-in-TAV deployment is a re-intervention and is therefore included in 'treatment'.
- Coronary obstruction is not included because the most common consequences (myocardial infarction and death) are included.
- Ventricular septal perforation and mitral valve apparatus damage or dysfunction are not included because of relatively low occurrence rates of these events and limited data availability.



4

Contemporary outcomes after surgical aortic valve replacement with bioprostheses and allografts

Systematic review and meta-analysis

Simone A. Huygens, Mostafa M. Mokhles, Milad Hanif, Jos A. Bekkers,
Ad J.J.C. Bogers, Maureen P.M.H. Rutten-van Mölken, Johanna J.M. Takkenberg.

EJCTS. 2016;50(4):605-616

SUMMARY

Many observational studies have reported outcomes after surgical aortic valve replacement (AVR), but there are no recent systematic reviews and meta-analyses including all available bioprostheses and allografts. The objective of this study is to provide a comprehensive and up-to-date overview of the outcomes after AVR with bioprostheses and allografts reported in the last 15 years. We conducted a systematic literature review (PROSPERO register: CRD42015017041) of studies published between 2000-2015. Inclusion criteria were observational studies or randomized controlled trials reporting on outcomes of AVR with bioprostheses (stented or stentless) or allografts, with or without coronary artery bypass grafting (CABG) or valve repair procedure, with study population size n≥30 and mean follow-up length ≥5 years. Fifty-four bioprosthesis studies and fourteen allograft studies were included, encompassing 55,712 and 3,872 patients and 349,840 and 32,419 patient-years, respectively. We pooled early mortality risk and linearized occurrence rates of valve-related events, re-intervention and late mortality in a random-effects model. Sensitivity, meta-regression and subgroup analyses were performed to investigate the influence of outliers on the pooled estimates and to explore sources of heterogeneity. Funnel plots were used to investigate publication bias. Pooled early mortality risks for bioprostheses and allografts were 4.99% (95% confidence interval[CI], 4.44-5.62) and 5.03% (95%CI, 3.61-7.01), respectively. The late mortality rate was 5.70%/patient-year (95%CI, 4.99-5.62) for bioprostheses and 1.68%/patient-year (95%CI, 1.23-2.28) for allografts. Pooled re-intervention rates for bioprostheses and allografts were 0.75%/patient-year (95%CI, 0.61-0.91) and 1.87%/patient-year (95%CI, 1.52-2.31), respectively. There was substantial heterogeneity in most outcomes. Meta-regression analyses identified covariates that could explain the heterogeneity: implantation period, valve type, patient age, gender, pre-intervention New York Heart Association (NYHA) class III/IV, concomitant CABG, study design, and follow-up length. There is possible publication bias in all outcomes. This comprehensive systematic review and meta-analysis provides an overview of the outcomes after AVR with bioprostheses and allografts reported during the last 15 years. The results of this study can support patient and doctors in the prosthetic valve choice and can be used in microsimulation models to predict patient outcomes and estimate cost-effectiveness of AVR with bioprostheses or allografts compared with current and future heart valve prostheses.

INTRODUCTION

Heart valve substitutes available for surgical aortic valve replacement (AVR) can be broadly divided into mechanical and biological valves. Biological valves have the advantages that there is no need for lifelong anticoagulation medication and that the ticking sound of mechanical valves is absent. However, disadvantages of biological valves are a limited durability and subsequent risk of reoperation. The use of biological valves in the USA increased from 37.7% of all implanted valves during 1998-2001 to 63.6% during 2007-2011.[1]

Biological valves can be divided into bioprostheses (stented or stentless), allografts and autografts. Stented bioprostheses are the most frequently implanted biological valves.[2] Stentless bioprostheses are presumed to have better haemodynamics than stented bioprostheses and therefore might prevent prosthesis-patient mismatch and improve durability.[3] However, long-term outcomes indicated that the durability was not better than expected.[3] Allografts were hypothesized to have improved durability compared to bioprostheses because they are obtained from human donors. However, several studies have shown that the risk of reoperation for structural valve deterioration (SVD) is comparable or even higher than in bioprostheses.[4, 5] Therefore, bioprostheses that are readily available might be preferred. Currently, allografts are predominantly implanted in patients with acute infective endocarditis with perivalvular lesions.[6]

Many observational studies reported the long-term mortality and occurrence of valve-related events after AVR with biological valve prostheses. Grunkemeier et al. reviewed the long-term clinical results of various options for heart valve replacement, based on publications between 1989 and 1999.[7] There are also several systematic reviews and meta-analyses that analysed the outcomes of implantation with specific bioprostheses across several publications.[8, 9] However, to our knowledge there are no recent systematic reviews and meta-analyses that include all available bioprostheses and allografts. The objective of this study is to provide up-to-date estimates of reported outcomes after surgical AVR (especially long-term mortality, valve-related events and re-interventions) with bioprostheses and allografts reported during the last 15 years.

METHODS

Search strategy and selection of studies

This systematic review was conducted according to the PRISMA guidelines [10] and registered in the PROSPERO register (CRD42015017041) (see Supplemental material for the PRISMA checklist). On 17 February 2015, the Embase, Medline, Cochrane, Pubmed publisher and Google Scholar databases were searched using key words regarding aortic heart valve bioprostheses or allografts and outcomes (search terms are provided in Supplemental material). We limited our search to studies that were conducted in humans and published in the last 15 years (1 January 2000-17 February 2015). This time frame was selected to reflect recent outcomes of AVR. Two researchers (SH, MM) independently reviewed the results on titles and abstracts to determine whether the study met the inclusion criteria. In case of disagreement, an agreement was negotiated. The inclusion criteria were observational studies or randomized controlled trials (RCTs) reporting on the outcomes of AVR with bioprostheses or allografts with or without coronary artery bypass grafting (CABG) or any other valve repair procedure, but excluding other valve replacements (a maximum of 10% multiple valve replacements in the study population was allowed) with a minimum study population size $n \geq 30$, and minimum mean follow-up length of 5 years. Studies were excluded if they only reported results of a propensity matched population (because of less generalizability of the study population), if the mean or median follow-up length was not reported, or when they only reported early mortality risk and no event occurrence, re-operation or late mortality (because the main aim of this study was to report long-term outcomes after AVR). In case of multiple publications on the same patient population, the publication with most follow-up patient-years was generally included. Exceptions were studies that had less follow-up patient-years but reported more relevant data than the overlapping study. Two researchers (SH, MM) jointly decided whether the exception was justified. References of selected papers were cross-checked for other relevant studies.

Data extraction

Microsoft Office Excel 2010 (Microsoft Corp., Redmond, WA, USA) was used for data extraction. Data extraction of all included studies was performed independently by two researchers (SH, MH). In case of disagreement about extracted data, an agreement was negotiated. Study design, valve implantation period (in calendar years) and follow-up duration (mean and total patient-years) were documented. The following patient characteristics were registered: mean patient age at the time of surgery, proportion of male patients, concomitant procedures, pre- and postintervention New York Heart Association (NYHA) class, subcoronary allograft valve replacement and endocarditis as indication for surgery. If the total number of patient-years was not provided, mean (or

if mean was not reported; median) follow-up was multiplied by the reported number of patients. Occurrence of valve-related events, re-intervention and mortality was registered according to the "2008 AATS/EACTS/STS guideline for reporting morbidity and mortality after cardiac valvular operations".[11] The following valve-related events were registered: early mortality (≤30 days postoperatively or in-hospital), late mortality (>30 days postoperatively, divided into sudden unexpected unexplained death (SUUD), cardiac, and valve-related mortality), re-intervention (with the reasons for re-intervention), early event occurrence (≤30 days postoperatively or in-hospital) and late event occurrence (>30 days postoperatively). The included valve-related events were SVD, non-structural valve dysfunction (NSVD), valve thrombosis, thromboembolism, bleeding, and endocarditis. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event. When the occurrence of valve-related events was only reported as a linearized occurrence rate (LOR), the number of events that occurred in the study population was calculated by multiplying the LOR with the total follow-up patient-years. In studies where the results were reported separately for subgroups (such as pericardial/porcine or stented/stentless valve prostheses), the weighted mean of covariates for the total population was calculated and occurrence rates were summed. Authors were contacted when full text was not available or to request additional information when follow-up length and total follow-up patient-years or the proportion of multiple valve replacements were not reported.

Statistical analyses

Early risks of mortality and valve-related events and late LORs of valve-related events, re-intervention and mortality were calculated for each individual study and pooled on a logarithmic scale with the use of the inverse variance method in a random-effects model. In the random-effects model the Der Simonian and Laird method was used for estimating the between-studies variance.[12] The choice to use a logarithmic scale was verified by performing Shapiro-Wilk tests on aggregated data on study level to test the normality of the distributions in our meta-analysis (i.e. we did not test the normality of the distributions of the underlying individual patient data). Leave-one-out sensitivity analyses were performed to assess the influence of outliers in the early mortality risk, late mortality and re-intervention rates. The Cochrane Q statistic and I^2 statistic were used to assess heterogeneity between studies. The causes of heterogeneity were explored by performing univariable meta-regression in the main outcome measures: early mortality, late mortality, SVD, NSVD, valve thrombosis, thromboembolism, bleeding, endocarditis and re-intervention. The covariates that were explored for both bioprostheses and allografts were the start and end of the valve implantation period, study design, mean follow-up, mean patient age, proportion of male patients, proportion of patients undergoing concomitant procedures, proportion of patients

undergoing concomitant CABG, and proportion of patients in NYHA class III/IV before surgery. In addition, valve type (stented or stentless and porcine or pericardial) was explored in the bioprostheses review and the proportion of patients undergoing subcoronary valve replacement (instead of total root replacement) and endocarditis as indication for surgery were explored in the allografts review. Subsequently, we have performed subgroup analyses for stented versus stentless bioprostheses, retrospective versus prospective study design (including RCT), and studies including AVR with concomitant CABG versus studies that only included AVR without concomitant CABG to investigate the differences in the outcome measures between these subgroups. Finally, funnel plots were used to investigate publication bias.

The meta-analysis, heterogeneity tests, subgroup analysis and funnel plots were performed in Microsoft Office Excel 2010, Shapiro-Wilk tests using SPSS, and leave-one-out sensitivity and univariable meta-regression analyses using open-source meta-analysis software that uses R as the underlying statistical engine.[13]

RESULTS

Literature search

The literature search resulted in 5,756 studies on bioprostheses and 2,291 studies on allografts. After applying inclusion and exclusion criteria, 54 studies on bioprostheses and 14 studies on allografts were included in the systematic review (references provided in Supplemental material). The study selection processes are illustrated in the flowchart in Figure 1. We made one exception on the general rule to include the publication with the most follow-up patient years in case of overlapping study populations: Ashikhmina et al. [14] reported more relevant outcome measures (early mortality, late SVD and late mortality); therefore, this study was included instead of Said et al. [15] where more follow-up patient-years were included.

Study characteristics

Tables 1 and 2 provide an overview of studies included in the present study. In the bioprosthesis group, 55,712 patients were included, resulting in 349,840 follow-up patient years. The allograft group included 3,872 patients with 32,419 follow-up patient years. The pooled mean follow-up length was 6.7 years for bioprostheses and 8.5 years for allografts. The pooled mean patient age was 71.8 years for bioprostheses and 48.8 years for allografts. Concomitant procedures were performed in 51.9% of the patients in studies on bioprostheses and 28.0% of patients in studies on allografts. A common concomitant procedure is CABG, performed in 40.0% of the patients in studies on bioprostheses and 11.9% of the patients in studies on allografts.

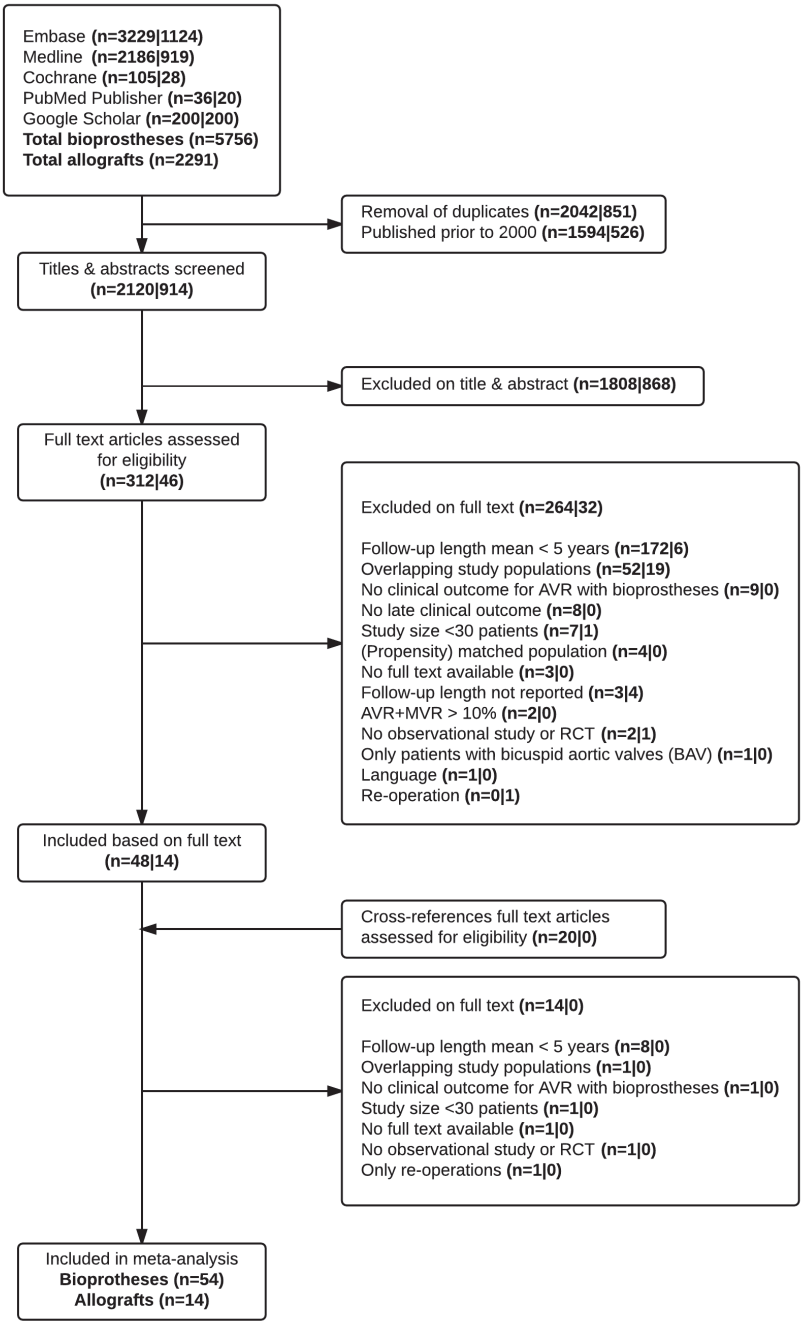


Figure 1. Flowchart of study selection. (n=bioprostheses|allografts). AVR: aortic valve replacement. MVR: mitral valve replacement. RCT: randomized controlled trial.

Study outcomes

The Shapiro-Wilk tests showed that the aggregated data on study level of the majority of the outcome measures had a normal distribution after log transformation (note that the distribution of the underlying individual patient data has not been tested). Table 3 gives the pooled estimates of early mortality and early valve-related events, late mortality, late valve-related events and re-intervention for bioprostheses and allografts. Estimates of the outcome measures for individual studies are provided in the Tables S1-S8.

Sensitivity analyses

The forest plots of the leave-one-out sensitivity analysis showed that there were no outliers in the meta-analysis of early mortality risk, late mortality and re-intervention rate in studies on bioprostheses. There was more variation in the outcome measures in studies on allografts. Figure 2 shows the forest plot of early mortality risk in studies on allografts. The other forest plots can be found in the Supplemental Material.

Heterogeneity

There was substantial heterogeneity according to the Cochrane Q and I^2 statistics in most outcome measures (Table 3), except for early valve thrombosis, early endocarditis, late valve thrombosis and re-intervention for valve thrombosis between studies on bioprostheses and late cardiac mortality, late bleeding, late endocarditis, and re-intervention for valve thrombosis and endocarditis between studies on allografts. The results of the univariable meta-regression analyses in the outcome measures with substantial heterogeneity between studies are described below and reported in Tables S9-S16.

Early mortality

Studies on bioprostheses with a more recent end of implantation period or studies with a high proportion of males reported lower early mortality risks. Studies on allografts with a more recent start of the implantation period report higher early mortality risks.

Late mortality

Studies on bioprostheses with a relatively old study population reported higher late mortality rates. In addition, studies on stentless bioprostheses reported lower late mortality rates compared with those on stented bioprostheses. Studies on allografts with a more recent start of implantation period, prospective studies, studies with a large proportion of concomitant procedures or studies with a large proportion of patients with pre-intervention NYHA class III/IV reported lower late mortality rates.

Late valve-related events

Studies on stentless bioprostheses reported higher SVD rates compared with those that report on stented bioprostheses. Prospective studies reported lower SVD rates compared with retrospective studies as did studies with a higher mean patient age. Studies on allografts with more recent start or end dates of the implantation period reported lower rates of SVD. Furthermore, studies with high mean follow-up duration, high proportion of patients with pre-intervention NYHA class III/IV or high proportion of patients undergoing subcoronary valve replacement reported relatively high SVD rates.

Relatively low NSVD rates were reported in studies on bioprostheses with a more recent end of implantation period or high proportion of males.

None of the covariates can explain the heterogeneity in thromboembolism, bleeding and endocarditis rates between studies on bioprostheses. Studies on allografts with more recent start or end dates of the implantation period reported lower thromboembolism rates. Furthermore, studies with a high proportion of patients undergoing concomitant CABG, with pre-intervention NYHA class III/IV or subcoronary valve replacements reported higher thromboembolism rates.

Re-intervention

Studies on bioprostheses with a high mean patient age reported lower rates for re-intervention. In addition, studies on stentless bioprostheses reported higher re-intervention rates compared with those on stented bioprostheses. Prospective studies on allografts reported lower re-intervention rates compared with retrospective studies.

Subgroup analyses

Table 4 summarizes the pooled estimates of patient and study characteristics and outcome measures in the subgroups of studies with stented (n=37) and stentless (n=13) bioprostheses. Noticeable are the differences in percentage of male patients (61.9% vs. 55.0% in studies on stented versus stentless bioprostheses, respectively) and the percentage of concomitant CABG procedures (41.5% vs. 28.9% in studies on stented versus stentless bioprostheses, respectively). The early mortality risk and late mortality rate are higher in studies on stented bioprostheses, whereas the SVD and re-intervention rates are higher in studies on stentless bioprostheses.

The results of the subgroup analyses comparing studies with retrospective versus prospective designs are reported in Tables S17-18. There were no large differences in outcome measures between retrospective and prospective studies; therefore, we can safely combine the outcomes of both types of studies in our meta-analysis.

Table 1. Overview of included publications on bioprostheses.

First author*	Year of publication	Implantation period	No. of patients	Type of valve		Study type	Mean follow-up, y	Mean age, y (range)	Concomitant CABG, n (%)
Akins	2002	1984-1997	469	Stented	Porcine + pericardial	Retrospective	5.1	75.0 (-)	469 (100)
Albert	2010	1996-2006	815	Stentless	Porcine	Retrospective	7.7	73.0 (-)	-
Amabile	2014	1997-2004	500	Stentless	Porcine	Prospective	5.9	74.5 (26-91)	120 (24)
Anselmi	2014	1994-2004	1,005	Stented	Porcine	Retrospective	8.5	74.7 (26-93)	147 (15)
Ashikhmina	2011	1993-2007	2,658	Stented	Porcine + pericardial	Prospective	5.0	78.0 (-)	1,409 (53)
Benetis	2014	1997-2012	167	Stentless	Porcine + pericardial	Prospective	5.0	72.5 (48-86)	53 (32)
Benhameid	2008	1982-1992	161	Stented	Pericardial	Retrospective	8.6	69.5 (60-94)	39 (24)
Biglioli	2004	1984-2000	327	Stented	Pericardial	Retrospective	6.0	67.2 (19-83)	75 (23)
Birla	2013	2001-2005	403	Stented	Porcine + pericardial	RCT	6.0	74.9 (40-91)	200 (50)
Bottio	2004	1992-2001	258	Stented	Porcine	Prospective	5.0	75.0 (45-91)	56 (22)
Bottio	2005	1970-1984	192	Stented	Porcine	Retrospective	12.3	48.5 (18-70)	13 (7)
Bourguignon	2015	1984-2008	2,758	Stented	Pericardial	Prospective	6.7	70.7 (16-91)	637 (23)
Celiento	2012	1995-2008	178	Stented	Porcine	Retrospective	5.7	74.0 (-)	25 (14)
Chan	2006	1992-1998	2,195	Stented	Porcine + pericardial	Retrospective	7.5	- (-)	955 (44)
Chan	2011	1976-2010	3,152	Stented	Porcine + pericardial	Prospective	5.8[3]	- (-)	1,631 (52)
Chiang	2014	1997-2004	1,466	Unknown	Porcine + pericardial	Retrospective	10.6[¥]	62.3 (50-69)	0 (0)
David	2008	1991-2004	357	Stentless	Porcine	Retrospective[1]	7.7	65.0 (22-84)	114 (32)
David	2010	1982-2004	1,134	Stented	Porcine	Prospective	12.4	67.0 (19-94)	572 (50)
de la Fuente	2003	1988-2000	215	Stented	Porcine + pericardial	Prospective	6.0	68.5 (24-81)	0 (0)
Dellgren	2002a	1984-1995	254	Stented	Pericardial	Retrospective	5.0	71.3 (25-87)	130 (51)
Dellgren	2002b	1990-2000	112	Stentless	Porcine	Prospective	5.5	78.5 (61-89)	35 (31)
Desai	2004	1992-2000	200	Stentless	Porcine	Retrospective	5.8	64.6 (33-82)	69 (35)
Eichinger	2008	1985-1996	455	Stented	Porcine	Retrospective	8.2	72.5 (-)	171 (38)
Flameng	2014	1991-2005	648	Stented + stentless	Porcine + pericardial	Retrospective	7.5	73.8 (-)	318 (49)
Forcillo	2013	1981-2011	2,405	Stented	Pericardial	Retrospective	6.0	71.0 (18-90)	1,010 (42)
Franzen	2001	1989-1996	90	Stented	Pericardial	Retrospective	5.0	78.0 (58-84)	37 (41)
Frapier	2002	1986-1990	90	Stented	Porcine	Retrospective	6.6	72.6 (36-86)	18 (20)
Gansera	2014	1993-2007	272	Stented	Porcine	Retrospective	6.1	76.8[¥] (31-91)	0 (0)
Glaser	2014	2002-2010	1,219	Stented	Porcine + pericardial	Retrospective	5.0	73.6 (-)	-
Grocott-Mason	2000	1969-1993	47	Stented	Porcine	Retrospective	5.2	70.2 (43-85)	20 (43)
Grunkemeier	2012	1974-2010	2,955	Stented	-	Prospective	5.3	73.1 (-)	1377 (47)

Table 1. Continued

First author*	Year of publication	Implantation period	No. of patients	Type of valve		Study type	Mean follow-up, y	Mean age, y (range)	Concomitant CABG, n (%)
Jamieson	2001	1986-1996	836	Stented	Porcine	Retrospective	6.2	67.0 (9-91)[4]	-
Jamieson	2006	1984-2001	1,430	Stented	Pericardial[2]	Retrospective	5.4	69.5 (16-90)	257 (18)
Jamieson	2011	1994-2000	797	Stented	Porcine	Prospective	7.5	69.0 (21-88)	362 (45)
Johnston	2015	1982-2011	12,569	Stented	Pericardial	Prospective	6.5	71.0 (18-91)	6,033 (48)
Kurlansky	2007	1976-1999	438[5]	Stented	Porcine	Retrospective	5.3	77.0 (65-91)	0 (0)
Le Tourneau	2007	1989-1993	222	Unknown	Unknown	Retrospective	7.3	73.0 (-)	32 (14)
Lehmann	2011	1996-1999	225	Stented + stentless	Porcine	Prospective	8.5	72.3 (-)	0 (0)
Luciani	2001	1992-1996	106	Stentless	Porcine	Retrospective	5.8	70.0 (26-83)	27 (25)
McClure	2010	1991-2002	1,000	Stented	Pericardial	Retrospective	6.0	74.1 (19-95)	443 (44)
Merie	2012	1997-2009	4,075	Unknown	Unknown	Retrospective	6.6¥	74.6 (18-95)	1,858 (46)
Minakata	2014	1986-2001	574	Stented	Pericardial	Retrospective	8.2	71.9 (21-89)	114 (20)
Minami	2005	1985-2004	1,516	Stented	Pericardial	Retrospective	5.5	75.6 (16-92)	811 (54)
Mohammedi	2014	1993-2013	531	Stentless	Porcine	Prospective	10.3	67.6 (-)	174 (33)
Myken	2009	1983-2003	1,518	Unknown	Porcine	Retrospective	6.0	70.8 (16-88)	638 (42)
Pavoni	2007	1994-2004	185	Stentless	Porcine	Retrospective	5.4	72.0 (-)	52 (28)
Polvani	2005	1992-1994	67	Stentless	Porcine	Retrospective	9.8	67.9 (22-83)	2 (3)
Rizzoli	2006	1983-2002	809	Stented	Porcine	Retrospective	6.4	68.0 (-)	238 (29)
Ruggieri	2012	1983-1994	1,002	Stented	Pericardial	Prospective	13.7	74.3 (-)	151 (15)
Sakamoto	2006	1991-2002	53	Stented	Pericardial	Retrospective	7.1	68.8 (-)	4 (8)
Sansone	2014	1996-2004	138	Stented + stentless	Porcine + pericardial	Retrospective	10.4	62.0 (-)	0 (0)
Silberman	2008	1993-2004	163	Stented + stentless	-	Retrospective	5.1	71.0 (25-87)	73 (45)
Sjögren	2006	1990-1993	152	Stented	Pericardial	Retrospective	6.2	79.5 (75-91)	74 (49)
Stanger	2014	2005-2009	149	Stentless	Pericardial	Retrospective	5.5	73.6 (47-87)	79 (53)
Pooled			**55,712**				**6.7**	**71.8**	**21,115 (40)**

CABG: coronary artery bypass grafting. RCT: randomized controlled trial. "-": variable not reported. *The full references of the included studies are provided in the supplemental material. ¥: median. [1]First 174 patients were prospectively followed, remaining patients retrospectively. [2]Only the subgroup of patients that received a Carpentier Edwards Perimount pericardial valve was included. The subgroup of patients that received a Carpentier-Edwards supra-annular porcine valve was excluded because of overlap with the patient population from another included study. [3]Mean follow-up of total population, including MVR patients. [4]Mean and range age of total population, including MVR patients. [5]Only the subgroup of patients with isolated AVR (without concomitant CABG) was included.

Table 2. Overview of included publications on allografts.

First author*	Year of publication	Implantation period	No. of patients	Surgical technique, % subcoronary/root replacement		Study design	Mean follow-up, y	Mean age, y (range)	Endocarditis as indication for surgery, n (%)	Concomitant CABG, n (%)
Ali	2010	1991-2001	217	60	40	Retrospective	6.4	62.0 (-)	-	43 (20)
Ganguly	2004	1990-1998	58[1]	83	17	Retrospective	5.5	63.0 (22-88)	8 (14)	12 (21)
Grocott-Mason	2000	1969-1993	381	92	8	Retrospective	9.8	53.8 (15-84)	-	60 (16)
Hickey	2007	1973-1983	200	100	0	Retrospective	15.8	- (-)	5 (3)	4 (2)
Kaya	2005	1989-2003	213	0	100	Retrospective	5.8	51.3 (14-79)	125 (59)	17 (8)
Killian	2010	1992-?	351	21	79	Prospective	15.2	51.6 (12-84)	62 (18)	42 (12)
Kitamura	2011	1990-?	40	58	43	Retrospective	9.9	50.4 (16-73)	18 (45)	5 (12.5)
Mokhles	2014	1987-2010	356	26	74	Prospective	10.8	44.4 (16-83)	-	34 (10)
O'Brien	2001	1969-1998	1,022	66[2]	34	Retrospective	7.3	46.6 (1-80)	-	110 (11)
Ruzmetov	2012	1990-2011	44	0	100	Retrospective	7.4	18.8 (0-40)	12 (27)	-
Smedira	2006	1987-2000	744	3	97	Retrospective	5.6	49.0 (18-44)	186 (25)	112 (15)
Talwar	2005	1994-2003	154	71	29[3]	Prospective	5.2	28.8 (5-68)	4 (3)	6 (4)
Vuran	2012	?-?	40	0	100	Retrospective	5.6	40.0¥ (0-79)	20 (50)	-
Wasywich	2003	1980-1989	52	-	-	Retrospective	6.8	73.0¥ (70-80)	-	-
Pooled			**3,872**	**45**	**55**		**8.5**	**48.8**	**23.9**	**445 (12)**

CABG: coronary artery bypass grafting. "-": variable not reported. *The full references of the included studies are provided in the supplemental files. ¥: median. 1Including pulmonary homografts (n=11). 2Including intraluminal cylinder implant (n=35). 3Including conduits replacing the aortic valve and ascending aorta (n=6).

Table 3. Pooled estimates of outcomes after AVR with bioprostheses and allografts.

	Bioprostheses	Reported in n studies	I^2, % ($\chi 2$ P-value)	Allografts	Reported in n studies	I^2, % ($\chi 2$ P-value)
Study characteristics						
No. of studies	54			14		
No. of patients	55,712			3,872		
Mean follow-up, y ±SD	6.7 ± 4.7	54		8.5 ± 3.0	14	
Mean age, y ±SD	71.8 ± 9.3	52		48.8 ± 13.0	13	
Male, %	61.0	48		69.4	13	
Concomitant CABG, %	40,1	50		12.3	9	
Early mortality, %						
Early mortality	4.99 (4.44-5.62)	48	81 (0.000)	5.03 (3.61-7.01)	14	73 (0.000)
Early valve-related events, %						
SVD	0.58 (0.01-25.32)	3	91 (0.000)		0	
NSVD		2			0	
Valve thrombosis	0.34 (0.15-0.79)	3	0 (0.488)		0	
Thromboembolism	2.95 (1.55-5.60)	7	92 (0.000)		0	
Reexploration for bleeding	4.06 (2.93-5.63)	14	92 (0.000)		1	
Endocarditis	0.22 (0.07-0.70)	4	36 (0.194)		1	
Late mortality, %/year						
Late mortality	5.70 (4.99-6.53)	47	99 (0.000)	1.68 (1.23-2.28)	10	86 (0.000)
Cardiac late mortality	2.49 (1.95-3.18)	29	98 (0.000)	1.03 (0.88-1.19)	8	0 (0.760)
Valve-related late mortality	0.92 (0.74-1.15)	33	94 (0.000)	0.41 (0.29-0.58)	9	51 (0.037)
SUUD	0.15 (0.09-0.26)	21	90 (0.000)		2	
Late valve-related events, %/year						
SVD	0.60 (0.47-0.76)	37	93 (0.000)	2.26 (1.02-4.97)	3	90 (0.000)
NSVD	0.20 (0.13-0.32)	20	88 (0.000)		1	
Valve thrombosis	0.04 (0.03-0.07)	13	0 (0.651)		0	
Thromboembolism	1.10 (0.83-1.47)	36	97 (0.000)	0.46 (0.20-1.08)	5	93 (0.000)
Bleeding	0.44 (0.30-0.65)	31	96 (0.000)	0.15 (0.09-0.25)	3	0 (0.548)
Endocarditis	0.38 (0.32-0.44)	35	57 (0.000)	0.42 (0.31-0.58)	5	28 (0.236)
Re-interventions, %/year						
Total	0.75 (0.61-0.91)	47	95 (0.000)	1.87 (1.52-2.31)	13	80 (0.000)
Valve-related	0.72 (0.60-0.86)	45	94 (0.000)	1.85 (1.49-2.29)	13	81 (0.000)
SVD	0.42 (0.33-0.54)	37	92 (0.000)	1.15 (0.77-1.70)	8	90 (0.000)
NSVD	0.11 (0.07-0.17)	28	74 (0.000)	0.13 (0.05-0.32)	7	73 (0.001)
Valve thrombosis	0.03 (0.02-0.05)	25	0 (0.642)	0.02 (0.01-0.06)	8	0 (0.655)
Endocarditis	0.19 (0.16-0.23)	31	46 (0.004)	0.27 (0.19-0.38)	9	36 (0.128)

SVD: structural valve deterioration. NSVD: non-structural valve dysfunction. SUUD: sudden unexpected unexplained death. CABG: coronary artery bypass grafting. 95% CIs of the pooled estimates are provided in parentheses. Pooled estimates are only reported when ≥3 studies reported the outcome measure. Total numbers of early and late valve-related events are not reported because few studies reported all valve-related events.

Table 4. Subgroup analysis stented versus stentless bioprostheses.

	Stented bioprostheses	Reported in n studies	Stentless bioprostheses	Reported in n studies
Study characteristics				
No. of studies	37		13	
No. of patients	44,208		3,412	
Mean follow-up, y ±SD	6.6 ± 4.9	37	7.4 ± 3.3	13
Mean age, y ±SD	71.9 ± 9.5	35	70.6 ± 8.4	13
Male, %	61.9	31	55.0	13
Concomitant CABG, %	41.5	34	28.9	11
Early mortality, %				
Early mortality	5.15 (4.43-5.98)	32	4.17 (3.08-5.65)	11
Early valve-related events, %				
SVD	0.03 (0.00-0.19)	2		1
NSVD		2		1
Valve thrombosis,	0.20 (0.06-0.68)	3		1
Thromboembolism	1.41 (0.52-3.81)	5	3.64 (0.40-32.71)	2
Reexploration for bleeding	3.62 (2.53-5.16)	11	6.96 (5.08-9.55)	5
Endocarditis	0.10 (0.04-0.24)	3		2
Late mortality, %/year				
Late mortality	6.01 (5.10-7.08)	32	4.56 (3.70-5.61)	12
Late valve-related events, %/year				
Cardiac late mortality	2.31 (1.73-3.09)	19	2.21 (1.50-3.26)	8
Valve-related late mortality	0.93 (0.74-1.16)	24	0.89 (0.43-1.84)	8
SUUD	0.19 (0.11-0.35)	16	0.05 (0.02-0.18)	5
SVD	0.48 (0.38-0.62)	26	1.10 (0.65-1.86)	9
NSVD	0.16 (0.10-0.27)	18	0.33 (0.06-1.77)	3
Valve thrombosis	0.04 (0.02-0.07)	11		2
Thromboembolism	1.04 (0.83-1.30)	26	0.99 (0.66-1.47)	8
Bleeding	0.43 (0.32-0.57)	21	0.31 (0.14-0.70)	7
Endocarditis	0.34 (0.27-0.43)	25	0.43 (0.33-0.58)	8
Re-interventions, %/year				
Total	0.65 (0.51-0.83)	34	1.06 (0.77-1.46)	12
Valve-related	0.63 (0.51-0.78)	32	0.99 (0.69-1.41)	12
SVD	0.33 (0.24-0.44)	24	0.82 (0.57-1.19)	11
NSVD	0.08 (0.05-0.13)	19	0.27 (0.14-0.50)	9
Valve thrombosis	0.03 (0.02-0.04)	19	0.04 (0.01-0.10)	8
Endocarditis	0.16 (0.13-0.20)	22	0.24 (0.15-0.37)	9

SVD: structural valve deterioration. NSVD: non-structural valve dysfunction. SUUD: sudden unexpected unexplained death. 95% confidence intervals of the pooled estimates are provided in parentheses. Pooled estimates are only reported when ≥3 studies reported the outcome measure. Total numbers of early and late valve-related events are not reported because few studies reported all valve-related events.

Table S19 presents the results of the subgroup analysis of studies on bioprostheses without concomitant CABG (n=6) versus with concomitant CABG (n=45). The mean patient age was higher in the AVR with concomitant CABG group (72.1 versus 67.4 years in AVR with CABG versus AVR without concomitant CABG, respectively). The late mortality rate is higher in the studies including concomitant CABG (5.83%/patient-year) than in those including only isolated AVR (4.81%/patient-year). In addition, the rates of late SVD, bleeding, endocarditis and re-intervention are higher in studies on AVR with CABG than AVR without CABG. This subgroup analysis could not be performed for the studies on allografts because none of the studies reported outcomes of AVR without CABG.

Publication bias

The funnel plots showed evidence of possible publication bias in all outcome measures. Smaller studies with relatively high event rate estimates seemed to be less likely to be published. Figure 3 shows the funnel plot of re-intervention rate in studies on bioprostheses. The other funnel plots can be found in the Supplementary Material.

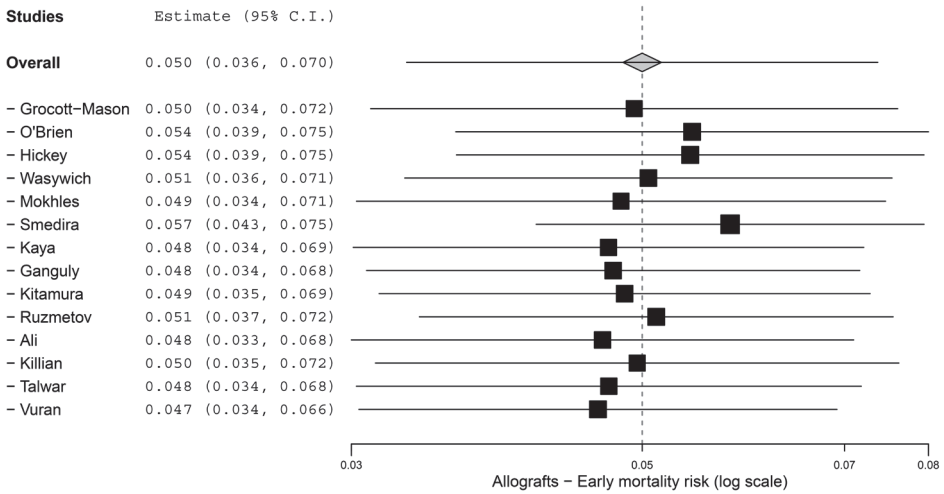


Figure 2. Forest plot of leave-one-out-analysis of early mortality risk in studies on allografts.
CI: confidence interval.

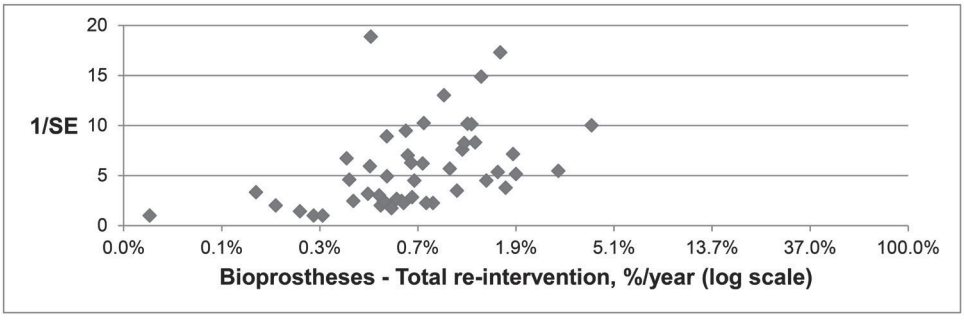


Figure 3. Funnel plot of total re-intervention rate in studies on bioprostheses.

DISCUSSION

This is the first comprehensive systematic review and meta-analysis of the outcomes after surgical AVR with bioprostheses and allografts reflecting an overview of reported outcome after biological AVR in the past 15 years. In this study, we have screened over 8000 studies and included almost 70 studies from which we extracted data on the outcomes after AVR. The results of this study can inform patients and doctors about the expected outcomes after AVR with bioprostheses or allografts and thereby support prosthetic valve selection. Furthermore, we will use the results of this study in microsimulation models to predict individual patient outcomes and estimate cost-effectiveness of AVR with bioprostheses or allografts. Finally, the results can be used as a benchmark for the performance of new alternative interventions for conventional surgical AVR, such as sutureless valves, transcatheter aortic valve implantation (TAVI), and in the future, potentially in situ tissue-engineered heart valves.

Patient and study characteristics

There are several differences in the patient and study characteristics between the studies on bioprostheses and allografts. Patients in studies on bioprostheses are older (mean age: 71.8 versus 48.8 years in studies on bioprostheses versus allografts), they have more concomitant CABG (40.0% versus 11.9% in studies on bioprostheses versus allografts) and the mean follow-up duration of studies on bioprostheses is shorter than for allografts (6.7 versus 8.5 years in studies on bioprostheses versus allografts). These differences make it impossible to draw meaningful conclusions about the differences in performance between bioprostheses and allografts based on the results of this study.

In many institutions root replacement instead of subcoronary valve replacement is the technique of choice for implanting allografts in the aortic position since the mid-1990s.[4, 16, 17] This trend is also reflected in our review where studies with a larger proportion of root replacement as surgical technique are generally studies with a more recent implantation period.

Early mortality

Bioprostheses

The early mortality risk after AVR with bioprostheses is lower in recent years which reflects improvements in the past decades in diagnosis and perioperative management of AVR patients.

Our results indicated that studies on bioprostheses with a high proportion of male patients reported lower early mortality risk and NSVD rate. The relative worse outcomes for women may be caused by the different preoperative risk profile compared to men:

women undergoing AVR are older, more symptomatic (i.e. advanced NYHA class), have smaller body surface areas, more comorbidities and more often require emergency operations than men.[18-20] Delayed presentation of valve problems and/or later referral of women to cardio-thoracic surgery may explain some of the differences in risk profile.[19] There is some controversy about the impact of these risk profile differences on the outcomes after AVR between men and women. Some studies found an increased early mortality risk in women undergoing AVR with concomitant CABG [19, 21], but there is no evident association between gender and early mortality after isolated AVR.[18, 21, 22]

Allografts

More recent studies on AVR with allografts reported a relatively high early mortality risk. A possible explanation is that the indication for using allografts for AVR has changed over time from a broad range of patients to mostly complex patients with active endocarditis.[4, 6] Indeed, in this review, three relatively recent studies with endocarditis in more than 40% of the patients reported relatively high early mortality risks.[23-25]

Early valve-related events

Bioprostheses

The results of our study reflect low risks for most early events after AVR with bioprostheses, with bleeding and thromboembolism being most common. They reflect that AVR is a safe procedure; however, these low risks can also reflect underreporting since most included studies did not report early event occurrence. Of note, although we reported an early event risk for endocarditis during the first postoperative month, the risk of experiencing endocarditis still increases until 6 months postoperatively after which it reaches a plateau close to zero.[26]

Allografts

Occurrences of early valve-related events after AVR with allografts were not or rarely reported.

Late mortality

This review nicely illustrates that late deaths after AVR are only in part cardiac, and valve-related and SUUDs comprise only part of cardiac mortality. The remaining non-valve related cardiac mortality can be ascribed to the excess mortality risk in patients after AVR, due to underreporting of valve-related events and left ventricular dysfunction associated with heart valve disease.[27-29]

Bioprostheses

Our meta-regression confirmed the commonly reported finding that higher patient age at implant is associated with higher risk of late mortality after AVR with bioprostheses.[14, 30, 31]

Allografts

For allografts, there was a lower late mortality in the studies with a high proportion of patients with pre-intervention NYHA class III/IV. This seems counterintuitive, but might be explained by the fact that the indication in most patients receiving allografts is endocarditis, which is often accompanied with a worse pre-intervention NYHA class. Mokhles et al. have shown that the late mortality of hospital survivors after AVR for endocarditis is comparable with the general population.[32] This indicates that although these patients have a worse functional class before surgery, after surgery their endocarditis is cured and their mortality hazard returns to that of the general population. This can also explain why the late mortality rate is lower in studies on allografts with a more recent implantation period; in recent years, the indication for using allografts for AVR is often endocarditis.[4, 6] Indeed, three relatively recent studies in this review, where the indication for surgery was endocarditis in more than 40% of the patients, reported relatively low late mortality rates.[23-25] Furthermore, the low mean age of two studies with a high proportion of concomitant procedures [33, 34], might explain why studies with a high proportion of concomitant procedures report lower late mortality rates.

Surprisingly, prospective studies on allografts reported lower late mortality rates than retrospective studies. This observation is probably caused by more common use of prospective design in more recent years. Indeed, three 'old' retrospective studies (studies where the implantation period ended before 2000) [35-37] in this review report relatively high late mortality rates.

Late valve-related events

Bioprostheses

For bioprostheses, the most commonly reported late valve-related event was not SVD but thromboembolism, reflecting the advanced age of the patient population and the common occurrence of atrial fibrillation in this age group. The occurrence of SVD was less than 1% per year and more common in studies with a lower mean patient age, which confirms previous observations.[26]

Prospective studies on bioprostheses reported lower SVD rates compared to retrospective studies. This was unexpected because one would expect that prospective studies report higher SVD rates because of more accurate patient follow-up. The most likely explanation for this counterintuitive observation is the more common use of prospective study design in more recent years which results in relatively short follow-up periods, while the occurrence of SVD increases over time.[26]

Allografts

For allografts, SVD was the most commonly occurring late valve-related event. In this review, the occurrence of endocarditis after AVR is low. This is remarkable because the indication for AVR with allografts is often endocarditis. These results confirm that allografts have a good resistance to infection.

In the meta-regression, several associations were observed related to late occurrence of different valve-related events after allograft AVR. However, given the observational design of studies included in the review, the small number of studies reporting late valve-related events after allograft AVR and the low event occurrence rates; these associations should be interpreted cautiously and will not be further discussed here.

Re-interventions

Bioprostheses

As would be expected, valve-related re-interventions in bioprostheses studies showed low occurrence rates and were usually for SVD, whereas endocarditis and NSVD were less common indications. Studies with a relatively old patient population reported lower re-intervention rates. This is in accordance with previous reports that show that older patients are less likely to be re-operated.[17, 38, 39]

Allografts

Valve-related re-interventions in allografts were most often for SVD, and to a lesser extent for NSVD or endocarditis. Prospective studies on allografts reported lower re-intervention rates compared with retrospective studies. The effect is probably caused by the more common use of prospective study design in more recent years. Indeed, 'old' retrospective studies in this review report slightly higher re-intervention rates.

Stented versus stentless bioprostheses

Although it should be noted that in stented bioprostheses studies the proportion of males is higher, as is the proportion of patients undergoing concomitant CABG, the results of the present study indicate that early mortality risk and late mortality rate appear lower in studies on stentless bioprostheses compared with stented bioprostheses. In contrast, we found that SVD and re-intervention rates appear higher

in studies on stentless bioprostheses compared with stented bioprostheses. The observed lower late mortality rate in stentless bioprostheses is in accordance with the hypothesis that the haemodynamic superiority of stentless bioprostheses results in survival benefits compared with stented bioprostheses [3] but may also be the result of patient selection. The lower late mortality rate in stentless bioprostheses studies makes it difficult to directly compare durability of stentless with that of stented bioprostheses as the risk of death competes with the risk of SVD and re-intervention.

Concomitant CABG

Many studies included AVR with concomitant CABG and therefore the results of our study do not reflect the outcomes after isolated AVR. To explore the influence of including studies reporting on outcomes of AVR with concomitant CABG (in a proportion of the patient population), we have performed a subgroup analysis in the studies on bioprostheses comparing the outcomes of studies including and excluding concomitant CABG. This subgroup analysis showed that there are differences in the outcomes of AVR with or without CABG. However, the differences were not statistically significant (i.e. the CIs of the subgroups overlapped). Furthermore, concomitant CABG is a common concomitant procedure with AVR and therefore, the results presented in our study are relevant for clinical practice.

Limitations

First, inherent limitations of meta-analyses and combining data from (retrospective) observational studies should be taken into consideration.[40] Secondly, selection bias (of patients included in the studies) might have influenced the study outcomes due to the nature of observational studies (i.e no randomized allocation of patients to treatment options). Thirdly, publication bias may have potentially led to underestimation of the pooled estimates when studies with relatively poor outcomes are not published. Fourthly, by reporting LORs, we assumed a constant hazard for the valve-related events and late mortality, while in fact the distributions of these events are time-related.[26] Fifthly, initially we wanted to provide separate results for different age groups. However, this was not possible because most studies included patients of all ages. Finally, there was substantial heterogeneity between studies in most outcome measures, which may potentially lead to inaccurate results. However, we pursued a thorough examination of possible sources of heterogeneity using univariable meta-regression analysis and we identified several covariates that may explain the heterogeneity between studies in outcome measures. We deliberately did not perform multivariable meta-regression analysis because the underlying data was based on observational studies.

CONCLUSION

This comprehensive systematic review and meta-analysis provided an overview of the outcomes after surgical AVR with bioprostheses and allografts during the last 15 years. The results of this systematic review and meta-analysis can support patients and doctors in the prosthetic valve choice and can be used in microsimulation models to predict patient outcomes and estimate the cost-effectiveness of AVR with bioprostheses or allografts compared with current and future heart valve prostheses.

Acknowledgements. We would like to thank Wichor Bramer, information specialist at the Medical Library of the Erasmus University Medical Center, for his help with drafting the search query and executing the systematic literature retrieval.

Funding. This work was supported by the Netherlands Cardio Vascular Research Initiative: The Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences.

Conflicts of interest. None.

REFERENCES

1. Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. *National trends in utilization and hospital outcomes of mechanical vs. bioprosthetic aortic valve replacements*. The Journal of Thoracic and Cardiovascular Surgery 2015.
2. Chambers J. *Prosthetic heart valves*. Int J Clin Pract 2014;**68**:1227-30.
3. Kobayashi J. *Stentless aortic valve replacement: an update*. Vascular health and risk management. 2011;**7**:345.
4. Takkenberg JJM, Klieverik LMA, Bekkers JA, Kappetein AP, Roos JW, Eijkemans MJC *et al. Allografts for aortic valve or root replacement: insights from an 18-year single-center prospective follow-up study*. Eur J Cardiothorac Surg 2007;**31**:851-59.
5. El-Hamamsy I, Clark L, Stevens LM, Sarang Z, Melina G, Takkenberg JJM *et al. Late outcomes following Freestyle versus homograft aortic root replacement. Results from a prospective randomized trial*. J Am Coll Cardiol 2010;**55**:368-76.
6. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H *et al. Guidelines on the management of valvular heart disease (version 2012) The Joint Task Force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)*. Eur Heart J 2012;**33**:2451-96.
7. Grunkemeier GL, Li H-H, Naftel DC, Starr A, Rahimtoola SH. *Long-term performance of heart valve prostheses*. Curr Probl Cardiol 2000;**25**:78-154.
8. Puvimanasinghe JPA, Steyerberg EW, Takkenberg JJM, Eijkemans MJC, van Herwerden LA, Bogers AJJC *et al. Prognosis after aortic valve replacement with a bioprosthesis: predictions based on meta-analysis and microsimulation*. Circulation 2001;**103**:1535-41.
9. Puvimanasinghe JPA, Takkenberg JJM, Eijkemans MJC, van Herwerden LA, Jamieson WRE, Grunkemeier GL *et al. Comparison of Carpentier-Edwards pericardial and supraannular bioprostheses in aortic valve replacement*. Eur J Cardiothorac Surg 2006;**29**:374-79.
10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA *et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration*. Ann Intern Med 2009;**151**:W-65-W-94.
11. Akins CW, Miller DC, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL *et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions*. Eur J Cardiothorac Surg 2008;**33**:523-28.
12. Borenstein M, Hedges LV, Higgins J, Rothstein HR. *A basic introduction to fixed-effect and random effects models for meta-analysis*. Research Synthesis Methods 2010;**1**:97-111.
13. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. *Closing the gap between methodologists and end-users: R as a computational back-end*. J Stat Softw 2012;**49**:1-15.
14. Ashikhmina EA, Schaff HV, Dearani JA, Sundt TM, Suri RM, Park SJ *et al. Aortic valve replacement in the elderly determinants of late outcome*. Circulation 2011;**124**:1070-78.

15. Said SM, Ashikhmina E, Greason KL, Suri RM, Park SJ, Daly RC *et al. Do pericardial bioprostheses improve outcome of elderly patients undergoing aortic valve replacement?* Ann Thorac Surg 2012;**93**:1868-75.
16. Mokhles MM, Rajeswaran J, Bekkers JA, Borsboom GJJM, Roos-Hesselink JW, Steyerberg EW *et al. Capturing echocardiographic allograft valve function over time after allograft aortic valve or root replacement*. The Journal of thoracic and cardiovascular surgery 2014;**148**:1921-28. e3.
17. Jamieson WR, Miyagishima RT, Burr LH, Lichtenstein SV, Fradet GJ, Janusz MT. *Carpentier-Edwards porcine bioprostheses: clinical performance assessed by actual analysis*. The Journal of heart valve disease 2000;**9**:530-35.
18. Hamed O, Persson PJ, Engel AM, McDonough S, Smith JM. *Gender differences in outcomes following aortic valve replacement surgery*. International Journal of Surgery 2009;**7**:214-17.
19. Ibrahim MF, Paparella D, Ivanov J, Buchanan MR, Brister SJ. *Gender-related differences in morbidity and mortality during combined valve and coronary surgery*. The Journal of Thoracic and Cardiovascular Surgery 2003;**126**:959-64.
20. Kulik A, Lam BK, Rubens FD, Hendry PJ, Masters RG, Goldstein W *et al. Gender differences in the long-term outcomes after valve replacement surgery*. Heart 2009;**95**:318-26.
21. Aranki SF, Rizzo RJ, Couper GS, Adams DH, Collins Jr JJ, Gildea JS *et al. Aortic valve replacement in the elderly. Effect of gender and coronary artery disease on operative mortality*. Circulation 1993;**88**:II17-23.
22. Fuchs C, Mascherbauer J, Rosenhek R, Pernicka E, Klaar U, Scholten C *et al. Gender differences in clinical presentation and surgical outcome of aortic stenosis*. Heart 2010;**96**:539-45.
23. Kaya A, Schepens MA, Morshuis WJ, Heijmen RH, Brutel De La Riviere A, Dossche KM. *Valve-related events after aortic root replacement with cryopreserved aortic homografts*. Ann Thorac Surg 2005;**79**:1491-95.
24. Kitamura S, Yagihara T, Kobayashi J, Nakajima H, Toda K, Fujita T *et al. Mid- to long-term outcomes of cardiovascular tissue replacements utilizing homografts harvested and stored at Japanese institutional tissue banks*. Surg Today 2011;**41**:500-09.
25. Vuran C, Simon P, Wollenek G, Ozker E, Aslim E. *Midterm results of aortic valve replacement with cryopreserved homografts*. Balkan Med J 2012;**29**:170-73.
26. Blackstone EH, Naftel DC, Turner Jr ME. *The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information*. Journal of the American Statistical Association 1986;**81**:615-24.
27. Kvidal P, Bergström R, Hörte L-G, Ståhle E. *Observed and relative survival after aortic valve replacement*. J Am Coll Cardiol 2000;**35**:747-56.
28. Steyerberg EW, Kallewaard M, Van Der Graaf Y, Van Herwerden LA, Habbema JDF. *Decision analyses for prophylactic replacement of the Björk-Shiley convexo-concave heart valve: an evaluation of assumptions and estimates*. Med Decis Making 2000;**20**:20-32.

29. van Geldorp MWA, Eric Jamieson WR, Kappetein AP, Ye J, Fradet GJ, Eijkemans MJC *et al. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk*. The Journal of thoracic and cardiovascular surgery 2009;**137**:881-86. e5.
30. Amabile N, Bical OM, Azmoun A, Ramadan R, Nottin R, Deleuze PH. *Long-term results of Freestyle stentless bioprosthesis in the aortic position: A single-center prospective cohort of 500 patients*. J Thorac Cardiovasc Surg 2014; 148:1903-11
31. Akins CW, Hilgenberg AD, Vlahakes GJ, MacGillivray TE, Torchiana DF, Madsen JC. *Results of bioprosthetic versus mechanical aortic valve replacement performed with concomitant coronary artery bypass grafting*. The Annals of thoracic surgery 2002;**74**:1098-106.
32. Mokhles MM, Ciampichetti I, Head SJ, Takkenberg JJM, Bogers AJJC. *Survival of surgically treated infective endocarditis: a comparison with the general Dutch population*. The Annals of thoracic surgery 2011;**91**:1407-12.
33. Ruzmetov M, Geiss DM, Shah JJ, Fortuna RS. *Autograft or allograft aortic root replacement in children and young adults with aortic valve disease: A single-center comparison*. Ann Thorac Surg 2012;**94**:1604-11.
34. Talwar S, Mohapatra R, Saxena A, Singh R, Kumar AS. *Aortic homograft: A suitable substitute for aortic valve replacement*. Ann Thorac Surg 2005;**80**:832-38.
35. Ganguly G, Akhunji ZA, Neethling WML, Hodge AJ. *Homograft aortic valve replacement - The experience of one unit*. Heart Lung Circul 2004;**13**:161-67.
36. Hickey E, Langley SM, Allemby-Smith O, Livesey SA, Monro JL. *Subcoronary allograft aortic valve replacement: parametric risk-hazard outcome analysis to a minimum of 20 years*. Ann Thorac Surg 2007;**84**:1564-70.
37. O'Brien MF, Harrocks S, Stafford EG, Gardner MAH, Pohlner PG, Tesar PJ *et al. The homograft aortic valve: A 29-year, 99.3% follow up of 1,022 valve replacements*. J Heart Valve Dis 2001;**10**:334-45.
38. Chan V, Malas T, Lapierre H, Boodhwani M, Lam BK, Rubens FD *et al. Reoperation of left heart valve bioprostheses according to age at implantation*. Circulation 2011;**124**:S75-S80.
39. Bourguignon T, Bouquiaux-Stablo AL, Candolfi P, Mirza A, Loardi C, May MA *et al. Very long-term outcomes of the carpentier-edwards perimount valve in aortic position*. Ann Thorac Surg 2015;99:831-7.
40. Ioannidis JP, Lau J. *Pooling research results: benefits and limitations of meta-analysis*. The Joint Commission journal on quality improvement 1999;**25**:462-69.

SUPPLEMENTAL MATERIAL

PRISMA checklist

Section/topic	#	Checklist item	Reported in chapter
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Summary
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. Web address), and, if available, provide registration information including registration number.	Search strategy and selection of studies
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale.	Search strategy and selection of studies
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Search strategy and selection of studies
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary files
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Search strategy and selection of studies
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data extraction
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made.	Data extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	-
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means).	Data extraction
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis.	Statistical analyses
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies).	Statistical analyses
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Statistical analyses

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations.	Table 1+2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplemental files (S1-S8)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3 and Supplemental files (S1-S8)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Heterogeneity and Supplemental files
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression [see Item 16]).	Sensitivity analyses, Heterogeneity, Publication bias and Supplemental files
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias), and at review-level (e.g. incomplete retrieval of identified research, reporting bias).	Limitations
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review.	Funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org.**

References included studies

Bioprosthesis studies reference 1 to 54.
Allografts studies reference 30 and 55 to 67.

1. Akins CW, Hilgenberg AD, Vlahakes GJ, MacGillivray TE, Torchiana DF, Madsen JC. *Results of bioprosthetic versus mechanical aortic valve replacement performed with concomitant coronary artery bypass grafting*. The Annals of thoracic surgery 2002;**74**:1098-106.
2. Albert A, Florath I, Rosendahl U, Ismail M, Hassanein W, Ennker J. *The Late impact of surgical skills and training on the subcoronary implantation of the Freestyle stentless bioprosthesis*. J Heart Valve Dis 2010;**19**:104-14.
3. Amabile N, Bical OM, Azmoun A, Ramadan R, Nottin R, Deleuze PH. *Long-term results of Freestyle stentless bioprosthesis in the aortic position: A single-center prospective cohort of 500 patients*. J Thorac Cardiovasc Surg 2014.
4. Anselmi A, Flecher E, Ruggieri VG, Harmouche M, Langanay T, Corbineau H *et al. Long-term results of the Medtronic Mosaic porcine bioprosthesis in the aortic position*. J Thorac Cardiovasc Surg 2014;**147**:1884-91.
5. Ashikhmina EA, Schaff HV, Dearani JA, Sundt TM, Suri RM, Park SJ *et al. Aortic valve replacement in the elderly determinants of late outcome*. Circulation 2011;**124**:1070-78.
6. Benetis R, Bolys R, Jakuska P, Ereminiene E, Jurgaitiene R, Kinduris S *et al. Long-term clinical and hemodynamic outcomes after operations on aortic root using stentless aortic valves*. Exp Clin Cardiol 2014;**20**:307-27.
7. Benhameid O, Jamieson WR, Castella M, Carrier M, Pomar JL, Germann E *et al. CarboMedics Mitroflow pericardial aortic bioprosthesis-performance in patients aged 60 years and older after 15 years*. The Thoracic and cardiovascular surgeon 2008;**56**:195-99.
8. Biglioli P, Spampinato N, Cannata A, Musumeci A, Parolari A, Gagliardi C *et al. Long-term outcomes of the Carpentier-Edwards pericardial valve prosthesis in the aortic position: effect of patient age*. J Heart Valve Dis 2004;**13**:S49-S51.
9. Birla R, Twine G, Unsworth-White J. *Randomized trial of carpentier-edwards supraannular prosthesis versus mosaic aortic prosthesis: 6 year results*. Ann Thorac Surg 2013;**95**:831-37.
10. Bottio T, Rizzoli G, Thiene G, Nesseris G, Casarotto D, Gerosa G. *Hemodynamic and clinical outcomes with the Biocor valve in the aortic position: An 8-year experience*. J Thorac Cardiovasc Surg 2004;**127**:1616-23.
11. Bottio T, Rizzoli G, Caprili L, Testolin L, Thiene G, Gerosa G. *Biological versus mechanical aortic prosthesis? A nineteen-year comparison in a propensity-matched population*. The Journal of heart valve disease 2005;**14**:493-500.
12. Bourguignon T, Bouquiaux-Stablo AL, Candolfi P, Mirza A, Loardi C, May MA *et al. Very Long-Term Outcomes of the Carpentier-Edwards Perimount Valve in Aortic Position*. Ann Thorac Surg 2015.
13. Celiento M, Ravenni G, Milano AD, Pratali S, Scioti G, Nardi C *et al. Aortic valve replacement with the medtronic mosaic bioprosthesis: A 13-year follow-up*. Ann Thorac Surg 2012;**93**:510-15.

14. Chan V, Jamieson WRE, Germann E, Chan F, Miyagishima RT, Burr LH *et al. Performance of bioprostheses and mechanical prostheses assessed by composites of valve-related complications to 15 years after aortic valve replacement*. The Journal of thoracic and cardiovascular surgery 2006;**131**:1267-73.
15. Chan V, Malas T, Lapierre H, Boodhwani M, Lam BK, Rubens FD *et al. Reoperation of left heart valve bioprostheses according to age at implantation*. Circulation 2011;**124**:S75-S80.
16. Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. *Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years*. JAMA 2014;**312**:1323-29.
17. David TE, Armstrong S, Maganti M. *Hancock II bioprosthesis for aortic valve replacement: The gold standard of bioprosthetic valves durability?* Ann Thorac Surg 2010;**90**:775-81.
18. David TE, Feindel CM, Bos J, Ivanov J, Armstrong S. *Aortic valve replacement with Toronto SPV bioprosthesis: Optimal patient survival but suboptimal valve durability*. J Thorac Cardiovasc Surg 2008;**135**:19-24.
19. De La Fuente A, Sanchez R, Imizcoz A, Fernandez JL, Olaz F, Moriones I. *Intact Medtronic and Carpentier Edwards S.A.V.: Clinical and hemodynamic outcomes over 13 years*. Cardiovasc Surg 2003;**11**:139-44.
20. Dellgren G, David TE, Raanani E, Armstrong S, Ivanov J, Rakowski H. *Late hemodynamic and clinical outcomes of aortic valve replacement with the Carpentier-Edwards perimount pericardial bioprosthesis*. J Thorac Cardiovasc Surg 2002;**124**:146-54.
21. Dellgren G, Eriksson MJ, Brodin LA, Radegran K. *Eleven years' experience with the Biocor stentless aortic bioprosthesis: Clinical and hemodynamic follow-up with long-term relative survival rate*. Eur J Cardio-thorac Surg 2002;**22**:912-21.
22. Desai ND, Merin O, Cohen GN, Herman J, Mobilos S, Sever JY *et al. Long-term results of aortic valve replacement with the St. Jude Toronto stentless porcine valve*. The Annals of thoracic surgery 2004;**78**:2076-83.
23. Eichinger WB, Hettich IM, Ruzicka DJ, Holper K, Schricker C, Bleiziffer S *et al. Twenty-Year Experience With the St. Jude Medical Biocor Bioprosthesis in the Aortic Position*. Ann Thorac Surg 2008;**86**:1204-10.
24. Flameng W, Rega F, Vercalsteren M, Herijgers P, Meuris B. *Antimineralization treatment and patient-prosthesis mismatch are major determinants of the onset and incidence of structural valve degeneration in bioprosthetic heart valves*. J Thorac Cardiovasc Surg 2014;**147**:1219-24.
25. Forcillo J, El Hamamsy I, Stevens LM, Badrudin D, Pellerin M, Perrault LP *et al. The perimount valve in the aortic position: Twenty-year experience with patients under 60 years old*. Ann Thorac Surg 2014;**97**:1526-32.
26. Franzen SF, Nylander E, Olin CL. *Aortic valve replacement with pericardial valves in patients with small aortic roots. Clinical results in a consecutive series of patients receiving 19 and 21 mm prostheses*. Scand Cardiovasc J 2001;**35**:114-18.
27. Frapier JM, Rouviere P, Razcka F, Aymard T, Albat B, Chaptal PA. *Influence of patient-prosthesis mismatch on long-term results after aortic valve replacement with a stented bioprosthesis*. J Heart Valve Dis 2002;**11**:543-51.

28. Gansera B, Hapfelmeier A, Brandl K, Spiliopoulos K, Gundling F, Eichinger W. *The mosaic bioprosthesis in the aortic position: 17 years' results*. Thorac Cardiovasc Surg 2014;**62**:26-34.
29. Glaser N, Franco-Cereceda A, Sartipy U. *Late survival after aortic valve replacement with the perimount versus the mosaic bioprosthesis*. Ann Thorac Surg 2014;**97**:1314-20.
30. Grocott-Mason RM, Lund O, Elwidaa H, Mazhar R, Chandrasakeran V, Mitchell AG *et al. Long-term results after aortic valve replacement in patients with congestive heart failure homografts vs prosthetic valves*. Eur Heart J 2000;**21**:1698-707.
31. Grunkemeier GL, Furnary AP, Wu Y, Wang L, Starr A. *Durability of pericardial versus porcine bioprosthetic heart valves*. J Thorac Cardiovasc Surg 2012;**144**:1381-86.
32. Jamieson WR, Lemieux MD, Sullivan JA, Munro IA, Metras J, Cartier PC. *Medtronic Intact porcine bioprosthesis experience to twelve years*. Ann Thorac Surg 2001;**71**:S278-81.
33. Jamieson WRE, Germann E, Aupart MR, Neville PH, Marchand MA, Fradet GJ. *15-year comparison of supra-annular porcine and PERIMOUNT aortic bioprostheses*. Asian Cardiovascular and Thoracic Annals 2006;**14**:200-05.
34. Jamieson WRE, Riess F-C, Raudkivi PJ, Metras J, Busse EFG, Goldstein J *et al. Medtronic Mosaic porcine bioprosthesis: assessment of 12-year performance*. The Journal of thoracic and cardiovascular surgery 2011;**142**:302-07. e2.
35. Johnston DR, Soltesz EG, Vakil N, Rajeswaran J, Roselli EE, Sabik JF, 3rd *et al. Long-Term Durability of Bioprosthetic Aortic Valves: Implications From 12,569 Implants*. Ann Thorac Surg 2015.
36. Kurlansky PA, Williams DB, Traad EA, Carrillo RG. *Surgical management of aortic valve disease in elderly patients with and without coronary artery disease: influence on quality of life*. J Cardiovasc Surg (Torino) 2007;**48**:215.
37. Le Tourneau T, Marechaux S, Vincentelli A, Ennezat PV, Modine T, Polge AS *et al. Cardiovascular risk factors as predictors of early and late survival after bioprosthetic valve replacement for aortic stenosis*. J Heart Valve Dis 2007;**16**:483-88.
38. Lehmann S, Walther T, Kempfert J, Leontyev S, Bakhtiary F, Rastan A *et al. Ten-year follow up after prospectively randomized evaluation of stentless versus conventional xenograft aortic valve replacement*. J Heart Valve Dis 2011;**20**:681-87.
39. Luciani GB, Santini F, Auriemma S, Barozzi L, Bertolini P, Mazzucco A. *Long-term results after aortic valve replacement with the Biocor PSB stentless xenograft in the elderly*. Ann Thorac Surg 2001;**71**:S306-10.
40. McClure RS, Narayanasamy N, Wiegerinck E, Lipsitz S, Maloney A, Byrne JG *et al. Late Outcomes for Aortic Valve Replacement With the Carpentier-Edwards Pericardial Bioprosthesis: Up to 17-Year Follow-Up in 1,000 Patients*. Ann Thorac Surg 2010;**89**:1410-16.
41. Merie C, Kober L, Skov Olsen P, Andersson C, Gislason G, Skov Jensen J *et al. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding*. J Am Med Assoc 2012;**308**:2118-25.
42. Minakata K, Tanaka S, Okawa Y, Shimamoto M, Kaneko T, Takahara Y *et al. Long-term outcome of the Carpentier-Edwards pericardial valve in the aortic position in Japanese patients*. Circ J 2014;**78**:882-89.

43. Minami K, Zittermann A, Schulte-Eistrup S, Koertke H, Körfer R. *Mitroflow synergy prostheses for aortic valve replacement: 19 years experience with 1,516 patients*. The Annals of thoracic surgery 2005;**80**:1699-705.
44. Mohammadi S, Kalavrouziotis D, Voisine P, Dumont E, Doyle D, Perron J *et al. Bioprosthetic valve durability after stentless aortic valve replacement: The effect of implantation technique*. Ann Thorac Surg 2014;**97**:2011-18.
45. Myken PSU, Bech-Hansen O. *A 20-year experience of 1712 patients with the Biocor porcine bioprosthesis*. J Thorac Cardiovasc Surg 2009;**137**:76-81.
46. Pavoni D, Badano LP, Ius F, Mazzaro E, Frassani R, Gelsomino S *et al. Limited long-term durability of the Cryolife O'Brien stentless porcine xenograft valve*. Circulation 2007;**116**:I307-I13.
47. Polvani G, Barili F, Dainese L, Muratori M, Porqueddu M, Sala A *et al. Long-term results after aortic valve replacement with the bravo 400 stentless xenograft*. Ann Thorac Surg 2005;**80**:495-501.
48. Rizzoli G, Mirone S, Ius P, Polesel E, Bottio T, Salvador L *et al. Fifteen-year results with the Hancock II valve: a multicenter experience*. The Journal of thoracic and cardiovascular surgery 2006;**132**:602-09. e4.
49. Ruggieri VG, Flecher E, Anselmi A, Lelong B, Corbineau H, Verhoye JP *et al. Long-term results of the carpentier-edwards supraannular aortic valve prosthesis*. Ann Thorac Surg 2012;**94**:1191-97.
50. Sakamoto Y, Hashimoto K, Okuyama H, Takakura H, Ishii S, Taguchi S *et al. Prevalence and avoidance of patient-prosthesis mismatch in aortic valve replacement in small adults*. Ann Thorac Surg 2006;**81**:1305-09.
51. Sansone F, Dato GMA, Zingarelli E, Ferrero E, Prot S, Ceresa F *et al. Long-term follow-up of stentless prosthesis*. J Cardiol 2014;**63**:365-72.
52. Silberman S, Oren A, Dotan M, Merin O, Fink D, Deeb M *et al. Aortic valve replacement: choice between mechanical valves and bioprostheses*. J Card Surg 2008;**23**:299-306.
53. Sjogren J, Gudbjartsson T, Thulin LI. *Long-term outcome of the Mitroflow pericardial bioprosthesis in the elderly after aortic valve replacement*. J Heart Valve Dis 2006;**15**:197.
54. Stanger O, Bleuel I, Reineke S, Banz Y, Erdoes G, Tevaearai H *et al. Pitfalls and premature failure of the Freedom SOLO stentless valve*. Eur J Cardiothorac Surg 2014:ezu473.
55. Ali A, Patel A, Ali Z, Abu-Omar Y, Freed D, Saeed A *et al. Medium to long-term clinical outcome following stentless aortic valve replacement: Comparison between allograft and xenograft valves*. Interact Cardiovasc Thorac Surg 2010;**11**:166-70.
56. Ganguly G, Akhunji ZA, Neethling WML, Hodge AJ. *Homograft aortic valve replacement - The experience of one unit*. Heart Lung Circul 2004;**13**:161-67.
57. Hickey E, Langley SM, Allemby-Smith O, Livesey SA, Monro JL. *Subcoronary Allograft Aortic Valve Replacement: Parametric Risk-Hazard Outcome Analysis to a Minimum of 20 Years*. Ann Thorac Surg 2007;**84**:1564-70.
58. Kaya A, Schepens MA, Morshuis WJ, Heijmen RH, Brutel De La Riviere A, Dossche KM. *Valve-related events after aortic root replacement with cryopreserved aortic homografts*. Ann Thorac Surg 2005;**79**:1491-95.

59. Kilian E, Fries F, Kowert A, Vogt F, Kreuzer E, Reichart B. *Homograft implantation for aortic valve replacement since 15 years: Results and follow-up*. Heart Surg Forum 2010;**13**:E238-E42.
60. Kitamura S, Yagihara T, Kobayashi J, Nakajima H, Toda K, Fujita T *et al. Mid- to long-term outcomes of cardiovascular tissue replacements utilizing homografts harvested and stored at Japanese institutional tissue banks*. Surg Today 2011;**41**:500-09.
61. Mokhles MM, Rajeswaran J, Bekkers JA, Borsboom GJJM, Roos-Hesselink JW, Steyerberg EW *et al. Capturing echocardiographic allograft valve function over time after allograft aortic valve or root replacement*. The Journal of thoracic and cardiovascular surgery 2014;**148**:1921-28. e3.
62. O'Brien MF, Harrocks S, Stafford EG, Gardner MAH, Pohlner PG, Tesar PJ *et al. The homograft aortic valve: A 29-year, 99.3% follow up of 1,022 valve replacements*. J Heart Valve Dis 2001;**10**:334-45.
63. Ruzmetov M, Geiss DM, Shah JJ, Fortuna RS. *Autograft or allograft aortic root replacement in children and young adults with aortic valve disease: A single-center comparison*. Ann Thorac Surg 2012;**94**:1604-11.
64. Smedira NG, Blackstone EH, Roselli EE. *Are allografts the biologic valve of choice for aortic valve replacement in nonelderly patients? Comparison of explantation for structural valve deterioration of allograft* …. The Journal of thoracic … 2006.
65. Talwar S, Mohapatra R, Saxena A, Singh R, Kumar AS. *Aortic homograft: A suitable substitute for aortic valve replacement*. Ann Thorac Surg 2005;**80**:832-38.
66. Vuran C, Simon P, Wollenek G, Ozker E, Aslim E. *Midterm results of aortic valve replacement with cryopreserved homografts*. Balkan Med J 2012;**29**:170-73.
67. Wasywich CA, Ruygrok PN, West TM, Haydock DA. *Extentend follow up after isolated aoratic valve replacement in the elderly*. Heart Lung Circul 2003;**12**:103-07.

Search terms per database

Bioprostheses

Embase.com

('aorta valve replacement'/de OR 'aorta valve prosthesis'/de OR ('heart valve prosthesis'/de AND 'aorta valve'/de) OR (aort* AND (valve*) NEAR/6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent*)):ab,ti) AND (xenograft/de OR (xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR 'Carpentier-Edwards' OR Shiley OR hancock) NEAR/6 (graft* OR transplant* OR prosthe* OR bioprosthe* OR valve* OR aort*))):ab,ti) OR ('heart valve bioprosthesis'/de OR 'Carpentier Edwards bioprosthesis'/de OR 'Hancock valve prosthesis'/de OR 'Mosaic bioprosthesis'/de OR (('Carpentier-Edwards' OR Shiley OR hancock OR freestyle* OR mosaic OR '3f enable' OR biocor OR 'toronto spv') NEAR/6 (valve* OR bioprosthe* OR prosthe*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND ('clinical study'/de OR 'case control study'/exp

OR 'clinical article'/de OR 'clinical trial'/exp OR 'intervention study'/de OR 'longitudinal study'/exp OR 'major clinical study'/de OR 'prospective study'/de OR 'retrospective study'/de OR mortality/de OR 'cardiovascular mortality'/de OR 'surgical mortality'/de OR 'treatment outcome'/exp OR survival/exp OR 'graft survival'/de OR 'quality of life'/de OR 'follow up'/de OR 'evaluation study'/de OR 'comparative effectiveness'/de OR reoperation/de OR (clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality NEAR/3 life) OR result* OR (follow* NEXT/1 up*) OR 'long-term' OR longterm OR death OR evaluat* OR effectiv* OR reoperat*):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Conference Paper]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim OR [Conference Review]/lim)

Medline (OvidSP)

(("heart valve prosthesis"/ AND "aortic valve"/) OR (aort* ADJ6 (valve*) ADJ6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent*)).ab,ti.) AND (heterografts/ OR (xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR "Carpentier-Edwards" OR Shiley OR hancock) ADJ6 (graft* OR transplant* OR prosthe* OR bioprosthe* OR valve* OR aort*))).ab,ti.) OR (((("Carpentier-Edwards" OR Shiley OR hancock OR freestyle* OR mosaic OR "3f enable" OR biocor OR "toronto spv") ADJ3 (valve* OR bioprosthe* OR prosthe*)).ab,ti.) NOT (exp animals/ NOT humans/) AND ("Clinical Trial".pt. OR exp "Case-Control Studies"/ OR "Intervention Studies"/ OR exp "Longitudinal Studies"/ OR exp mortality/ OR mortality.xs. OR exp "treatment outcome"/ OR survival/ OR "graft survival"/ OR "quality of life"/ OR (clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality ADJ3 life) OR result* OR (follow* ADJ up*) OR "long-term" OR longterm OR death OR evaluat* OR effectiv* OR reoperat*).ab,ti.) AND english.la. NOT (congresses OR Letters OR Notes OR Editorials).pt.

Cochrane

((aort* AND (valve*) NEAR/6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent*)):ab,ti) AND ((xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR 'Carpentier-Edwards' OR Shiley OR hancock) NEAR/6 (graft* OR transplant* OR prosthe* OR bioprosthe* OR valve* OR aort*))):ab,ti) OR (((('Carpentier-Edwards' OR Shiley OR hancock OR freestyle* OR mosaic OR '3f enable' OR biocor OR 'toronto spv') NEAR/3 (valve* OR bioprosthe* OR prosthe*)):ab,ti) AND ((clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR

surviv* OR (quality NEAR/3 life) OR result* OR (follow* NEXT/1 up*) OR 'long-term' OR longterm OR death OR evaluat* OR effectiv* OR reoperat*):ab,ti)

PubMed publisher

((("heart valve prosthesis"[mh] AND "aortic valve"[mh]) OR (aorta valve*[tiab] OR aortic valve*[tiab]) AND (replace*[tiab] OR transplant*[tiab] OR xenotransplant*[tiab] OR xenograft*[tiab] OR heterotransplant*[tiab] OR heterograft*[tiab] OR prosthe*[tiab] OR bioprosthe*[tiab] OR stent*[tiab]))) AND (heterografts[mh] OR (xenograft*[tiab] OR xenotransplant*[tiab] OR heterograft*[tiab] OR heterotransplant*[tiab] OR ((xeno*[tiab] OR hetero*[tiab] OR porcine*[tiab] OR swine[tiab] OR pig[tiab] OR bovine*[tiab] OR nonhuman[tiab] OR animal[tiab] OR calf[tiab] OR cow[tiab] OR Carpentier-Edwards[tiab] OR Shiley[tiab] OR hancock[tiab]) AND (graft*[tiab] OR transplant*[tiab] OR prosthe*[tiab] OR bioprosthe*[tiab] OR valve*[tiab] OR aort*[tiab])))) OR (((Carpentier-Edwards[tiab] OR Shiley[tiab] OR hancock[tiab] OR freestyle*[tiab] OR mosaic[tiab] OR 3f enable*[tiab] OR biocor[tiab] OR toronto spv*[tiab]) AND (valve*[tiab] OR bioprosthe*[tiab] OR prosthe*[tiab]))) NOT (animals[mh] NOT humans[mh]) AND ("Clinical Trial".pt. OR "Case-Control Studies"[mh] OR "Intervention Studies"[mh] OR "Longitudinal Studies"[mh] OR mortality[mh] OR mortality[sh] OR "treatment outcome"[mh] OR survival[mh] OR "graft survival"[mh] OR "quality of life"[mh] OR (clinical*[tiab] OR trial*[tiab] OR prospect*[tiab] OR retrospect*[tiab] OR longitudin*[tiab] OR mortali*[tiab] OR outcome*[tiab] OR failure*[tiab] OR surviv*[tiab] OR quality of life*[tiab] OR result*[tiab] OR follow up*[tiab] OR long-term*[tiab] OR longterm[tiab] OR death OR evaluat* OR effectiv* OR reoperat*[tiab])) AND english[la] AND publisher[sb]

Google scholar

"aorta|aortic valve replacement|prosthesis|transplantation" xenograft|xenotransplantation|heterograft|heterotransplantation|"Carpentier-Edwards"|hancock clinical|trial|intervention|longitudinal|prospective|retrospective|mortality|outcome|survival|follow-up

Allografts

Embase.com

('aorta valve replacement'/de OR 'aorta valve prosthesis'/de OR ('heart valve prosthesis'/de AND 'aorta valve'/de) OR (aort* AND (valve*) NEAR/6 (replace* OR transplant* OR homotransplant* OR homoiotransplant* OR allotransplant* OR prosthe* OR bioprosthe* OR stent*)):ab,ti) AND (allograft/de OR allotransplantation/de OR (allograft* OR homograft* OR allotransplant* OR homotransplant* OR ((allo OR allogen* OR homo* OR human*) NEAR/3 (graft* OR transplant* OR valve*)) OR (human NEAR/3 (donor* OR donat*))):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND ('clinical study'/de OR 'case

control study'/exp OR 'clinical article'/de OR 'clinical trial'/exp OR 'intervention study'/de OR 'longitudinal study'/exp OR 'major clinical study'/de OR 'prospective study'/de OR 'retrospective study'/de OR mortality/de OR 'cardiovascular mortality'/de OR 'surgical mortality'/de OR 'treatment outcome'/exp OR survival/exp OR 'graft survival'/de OR 'quality of life'/de OR 'follow up'/de OR 'evaluation study'/de OR 'comparative effectiveness'/de OR reoperation/de OR (clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality NEAR/3 life) OR result* OR (follow* NEXT/1 up*) OR 'long-term' OR longterm OR death OR evaluat* OR effectiv* OR reoperat*):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Conference Paper]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim OR [Conference Review]/lim)

Medline (OvidSP)

((("heart valve prosthesis"/ AND "aortic valve"/) OR (aort* ADJ6 (valve*) ADJ6 (replace* OR transplant* OR homotransplant* OR homoiotransplant* OR allotransplant* OR prosthe* OR bioprosthe* OR stent*)).ab,ti.) AND (allografts/ OR "Transplantation, Homologous"/ OR (allograft* OR homograft* OR allotransplant* OR homotransplant* OR ((allo OR allogen* OR homo* OR human*) ADJ3 (graft* OR transplant* OR valve*)) OR (human ADJ3 (donor* OR donat*))).ab,ti.) NOT (exp animals/ NOT humans/) AND ("Clinical Trial".pt. OR exp "Case-Control Studies"/ OR "Intervention Studies"/ OR exp "Longitudinal Studies"/ OR exp mortality/ OR mortality.xs. OR exp "treatment outcome"/ OR survival/ OR "graft survival"/ OR "quality of life"/ OR (clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality ADJ3 life) OR result* OR (follow* ADJ up*) OR "long-term" OR longterm OR death OR evaluat*).ab,ti.) AND english.la. NOT (congresses OR Letters OR Notes OR Editorials).pt.

Cochrane

((aort* AND (valve*) NEAR/6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent*)):ab,ti) AND ((allograft* OR homograft* OR allotransplant* OR homotransplant* OR ((allo OR allogen* OR homo* OR human*) NEAR/3 (graft* OR transplant* OR valve*)) OR (human NEAR/3 (donor* OR donat*))):ab,ti) AND ((clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality NEAR/3 life) OR result* OR (follow* NEXT/1 up*) OR 'long-term' OR longterm OR death OR evaluat*):ab,ti)

PubMed publisher

((“heart valve prosthesis”[mh] AND “aortic valve”[mh]) OR (aorta valve*[tiab] OR aortic valve*[tiab]) AND (replace*[tiab] OR transplant*[tiab] OR xenotransplant*[tiab] OR xenograft*[tiab] OR heterotransplant*[tiab] OR heterograft*[tiab] OR prosthe*[tiab] OR bioprosthe*[tiab] OR stent*[tiab]))) AND (allografts[mh] OR “Transplantation, Homologous”[mh] OR (allograft*[tiab] OR homograft*[tiab] OR allotransplant*[tiab] OR homotransplant*[tiab] OR ((allo[tiab] OR allogen*[tiab] OR homo*[tiab] OR human*[tiab]) AND (graft*[tiab] OR transplant*[tiab] OR valve*[tiab])) OR human donor*[tiab] OR human donat*[tiab])) NOT (animals[mh] NOT humans[mh]) AND (“Clinical Trial”.pt. OR “Case-Control Studies”[mh] OR “Intervention Studies”[mh] OR “Longitudinal Studies”[mh] OR mortality[mh] OR mortality[sh] OR “treatment outcome”[mh] OR survival[mh] OR “graft survival”[mh] OR “quality of life”[mh] OR (clinical*[tiab] OR trial*[tiab] OR prospect*[tiab] OR retrospect*[tiab] OR longitudin*[tiab] OR mortali*[tiab] OR outcome*[tiab] OR failure*[tiab] OR surviv*[tiab] OR quality of life*[tiab] OR result*[tiab] OR follow up*[tiab] OR long-term*[tiab] OR longterm[tiab] OR death OR evaluat*[tiab])) AND english[la] AND publisher[sb]

Google Scholar

“aorta|aortic valve replacement|prosthesis|transplantation”
homograft|homotransplantation|allograft|allotransplantation clinical|trial|intervention |longitudinal|prospective|retrospective|mortality|outcome|survival|follow-up

Results meta-analyses

Table S1. Pooled estimates of early mortality and valve-related events after AVR with bioprostheses.

Author and publication year	Early mortality, %	Early SVD, %	Early NSVD, %	Early valve thrombosis, %	Early thromboembolism, %	Re-exploration for bleeding, %	Early endocarditis, %
Akins 2002	3.84 (2.44-6.04)	-	-	-	4.48 (2.95-6.80)	-	-
Albert 2010	-	-	-	-	-	-	-
Amabile 2014	5.20 (3.58-7.56)	-	-	-	-	-	-
Anselmi 2014	5.01 (3.83-6.56)	-	-	0.40 (0.15-1.06)	-	-	0.10 (0.01-0.71)
Ashikhmina 2011	4.06 (3.38-4.89)	-	-	-	-	5.30 (4.52-6.23)	-
Benetis 2014	5.99 (3.28-10.92)	-	-	-	-	-	-
Benhameid 2008	7.45 (4.32-12.85)	-	-	-	-	-	-
Biglioli 2004	3.67 (2.11-6.39)	-	-	-	-	-	-
Birla 2013	4.47 (2.84-7.02)	-	-	-	-	-	-
Bottio 2004	6.20 (3.86-9.97)	-	-	-	0.39 (0.05-2.74)	-	-
Bottio 2005	10.94 (7.30-16.38)	-	-	-	-	-	-
Bourguignon 2015	2.79 (2.24-3.48)	0.02 (0.00-0.29)	0.18 (0.08-0.44)	-	1.05 (0.73-1.51)	0.33 (0.17-0.63)	0.11 (0.04-0.34)
Celiento 2012	3.93 (1.90-8.13)	-	-	-	-	3.93 (1.90-8.13)	-
Chan 2006	-	-	-	-	-	-	-
Chan 2011	-	-	-	-	-	-	-
Chiang 2014	-	-	-	-	-	-	-
David 2008	0.56 (0.14-2.23)	-	-	-	-	-	-
David 2010	3.97 (2.98-5.28)	-	-	-	-	-	-
de la Fuente 2003	6.05 (3.57-10.24)	-	-	-	-	4.19 (2.21-7.93)	-
Dellgren 2002a	4.33 (2.43-7.72)	-	-	-	3.94 (2.14-7.23)	5.91 (3.61-9.65)	-
Dellgren 2002b	7.14 (3.66-13.93)	-	-	-	8.04 (4.29-15.04)	6.25 (3.05-12.81)	0.89 (0.13-6.28)
Desai 2004	2.50 (1.05-5.94)	-	-	-	-	-	-
Eichinger 2008	5.27 (3.57-7.79)	-	-	-	-	-	-
Flameng 2014	3.65 (2.46-5.42)	-	-	-	-	-	-
Forcillo 2013	4.86 (4.08-5.81)	-	-	-	-	4.99 (4.19-5.94)	-
Franzen 2001	5.56 (2.37-13.02)	-	-	-	-	-	-
Frapier 2002	10.00 (5.38-18.59)	-	-	-	-	-	-
Gansera 2014	4.41 (2.54-7.67)	-	-	-	-	-	-

Table S1. Continued

Author and publication year	Early mortality, %	Early SVD, %	Early NSVD, %	Early valve thrombosis, %	Early thromboembolism, %	Re-exploration for bleeding, %	Early endocarditis, %
Glaser 2014	4.02 (3.06-5.29)	-	-	-	-	-	-
Grocott-Mason 2000	17.00 (9.04-31.97)	-	-	-	-	-	-
Grunkemeier 2012	4.40 (3.72-5.20)	-	-	-	-	-	-
Jamieson 2001	5.38 (4.05-7.15)	-	-	-	-	-	-
Jamieson 2006	2.80 (2.06-3.80)	-	-	-	-	-	-
Jamieson 2011	2.80 (1.86-4.22)	-	-	-	-	-	-
Johnston 2015	-	-	-	-	-	-	-
Kurlansky 2007	6.16 (4.28-8.88)	-	-	-	-	4.57 (2.98-7.01)	-
Le Tourneau 2007	8.56 (5.57-13.16)	8.56 (5.57-13.16)	-	-	-	-	-
Lehmann 2011	1.78 (0.67-4.70)	-	-	-	-	2.22 (0.93-5.29)	-
Luciani 2001	2.83 (0.93-8.63)	-	-	-	-	-	-
McClure 2010	7.20 (5.76-8.99)	-	-	-	-	5.80 (4.52-7.45)	-
Merie 2012	6.00 (5.31-6.78)	-	-	-	4.93 (4.31-5.64)	1.84 (1.47-2.30)	-
Minakata 2014	4.53 (3.11-6.59)	-	-	-	-	-	-
Minami 2005	6.53 (5.40-7.90)	-	-	-	-	-	-
Mohammedi 2014	3.77 (2.45-5.79)	-	-	-	-	8.10 (6.08-10.78)	-
Myken 2009	5.07 (4.08-6.31)	-	-	-	-	-	-
Pavoni 2007	5.41 (2.96-9.88)	-	-	-	-	-	-
Polvani 2005	0.75 (0.05-11.81)	0.75 (0.05-11.81)	0.75 (0.05-11.81)	0.75 (0.05-11.81)	0.75 (0.05-11.81)	5.97 (2.31-15.44)	0.75 (0.05-11.81)
Rizzoli 2006	5.44 (4.08-7.25)	-	-	0.12 (0.02-0.88)	-	-	-
Ruggieri 2012	11.28 (9.48-13.42)	-	-	-	-	-	-
Sakamoto 2006	-	-	-	-	-	-	-
Sansone 2014	5.80 (2.96-11.36)	-	-	-	-	8.70 (5.06-14.93)	-
Silberman 2008	6.75 (3.81-11.94)	-	-	-	-	-	-
Sjögren 2006	2.63 (1.00-6.92)	-	-	-	-	-	-
Stanger 2014	2.68 (1.02-7.06)	-	-	-	-	-	-
Pooled total	**4.99 (4.44-5.62)**	**0.58 (0.01-25.32)**	**0.21 (0.09-0.48)**	**0.34 (0.15-0.79)**	**2.95 (1.55-5.60)**	**4.06 (2.93-5.63)**	**0.22 (0.07-0.70)**
I^2, % (χ2 P-value)	**81 (0.000)**	**91 (0.000)**	**0 (0.338)**	**0 (0.488)**	**92 (0.000)**	**92 (0.000)**	**36 (0.194)**

95% confidence intervals provided in parentheses. SVD: structural valve deterioration. NSVD: non-structural dysfunction. "-": variable not reported. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event. [1]Early bleeding events with or without re-exploration.

Table S2. Pooled estimates of early mortality and valve-related events after AVR with allografts.

Author and publication year	Early mortality, %	Early SVD, %	Early NSVD, %	Early valve thrombosis, %	Early thromboembolism, %	Reexploration for bleeding, %	Early endocarditis, %
Ali 2010	8.29 (5.33-12.91)	-	-	-	-	-	-
Ganguly 2004	8.62 (3.73-19.93)	-	-	-	-	-	-
Grocott-Mason 2000	5.00 (3.23-7.75)	-	-	-	-	-	-
Hickey 2007	1.50 (0.49-4.61)	-	-	-	-	-	-
Kaya 2005	7.51 (4.69-12.03)	-	-	-	-	-	-
Killian 2010	4.84 (3.05-7.70)	-	-	-	-	-	-
Kitamura 2011	7.50 (2.53-22.27)	-	-	-	-	-	-
Mokhles 2014	5.90 (3.90-8.93)	-	-	-	-	12.92 (9.87-16.92)	-
O'Brien 2001	3.03 (2.14-4.29)	-	-	-	-	-	0.20 (0.05-0.78)
Ruzmetov 2012	1.14 (0.07-17.88)	-	-	-	-	-	-
Smedira 2006	0.27 (0.07-1.07)	-	-	-	-	-	-
Talwar 2005	7.79 (4.53-13.42)	-	-	-	-	-	-
Vuran 2012	12.50 (5.51-28.38)	-	-	-	-	-	-
Wasywich 2003	3.85 (0.99-14.97)	-	-	-	-	-	-
Pooled total	**5.03 (3.61-7.01)**	*	*	*	*	*	*
I^2, % ($\chi 2$ P-value)	**73 (0.000)**						

95% confidence intervals provided in parentheses. SVD: structural valve deterioration. NSVD: non-structural dysfunction. "-": variable not reported. *≤1 study reported this outcome measure. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event.

Table S3. Pooled estimates of late mortality after AVR with bioprostheses.

Author and publication year	Late mortality, %/y	Cardiac late mortality %/y	Valve-related late mortality, %/y	SUUD, %/y
Akins 2002	8.33 (7.29-9.52)	3.58 (2.90-4.41)	1.64 (1.20-2.24)	0.76 (0.48-1.20)
Albert 2010	6.46 (5.69-7.33)[1]	-	-	-
Amabile 2014	7.54 (6.65-8.55)	4.11 (3.45-4.89)	3.67 (3.05-4.41)	-
Anselmi 2014	7.18 (6.64-7.76)	1.85 (1.58-2.17)	0.63 (0.48-0.83)	-
Ashikhmina 2011	8.85 (8.38-9.35)	-	-	-
Benetis 2014	-	-	-	-
Benhameid 2008	6.09 (4.95-7.49)	-	-	-
Biglioli 2004	5.10 (4.17-6.23)	-	-	-
Birla 2013	5.42 (4.59-6.40)	2.11 (1.61-2.77)[1]	-	-
Bottio 2004	6.17 (4.96-7.69)	2.55 (1.80-3.61)	0.82 (0.44-1.53)	0.04 (0.00-0.66)
Bottio 2005	5.49 (4.64-6.49)	-	0.97 (0.65-1.46)	-
Bourguignon 2015	5.94 (5.61-6.29)	-	1.38 (1.22-1.56)	0.95 (0.82-1.10)
Celiento 2012	3.74 (2.74-5.11)	1.48 (0.89-2.44)	0.69 (0.33-1.44)	0.05 (0.00-0.79)
Chan 2006	-	-	1.04 (0.90-1.21)[1]	0.09 (0.06-0.15)[1]
Chan 2011	2.90 (2.67-3.15)[1]	0.82 (0.69-0.96)[1]	0.24 (0.18-0.32)[1]	-
Chiang 2014	2.07 (1.86-2.31)[1]	-	-	-
David 2008	2.89 (2.32-3.59)	1.39 (1.01-1.91)[1]	0.48 (0.28-0.82)[1]	0.02 (0.00-0.29)
David 2010	4.10 (3.79-4.44)	1.55 (1.36-1.77)	0.53 (0.43-0.67)	0.00 (0.00-0.06)
de la Fuente 2003	4.02 (3.06-5.27)	2.33 (1.63-3.34)	0.64 (0.32-1.28)	0.04 (0.00-0.64)
Dellgren 2002a	4.78 (3.72-6.14)	1.98 (1.01-1.91)	0.41 (0.17-0.99)	0.04 (0.00-0.66)
Dellgren 2002b	7.65 (5.74-10.20)	4.27 (2.89-6.32)	0.71 (0.27-1.89)	0.09 (0.01-1.42)
Desai 2004	2.68 (1.89-3.79)	1.30 (0.78-2.14)	0.86 (0.47-1.60)	0.04 (0.00-0.69)
Eichinger 2008	-	-	1.02 (0.73-1.43)	-
Flameng 2014	-	-	-	-
Forcillo 2013	4.69 (4.36-5.05)	2.22 (2.00-2.48)	0.71 (0.59-0.87)	0.28 (0.20-0.38)
Franzen 2001	4.13 (2.59-6.57)	2.18 (1.14-4.17)	0.49 (0.12-1.93)	0.12 (0.01-1.94)
Frapier 2002	9.11 (7.06-11.74)	4.38 (3.01-6.38)	2.02 (1.16-3.54)	0.67 (0.25-1.79)
Gansera 2014	-	-	0.66 (0.37-1.20)	-
Glaser 2014	6.14 (5.56-6.77)	0.01 (0.00-0.13)	0.01 (0.00-0.13)	0.01 (0.00-0.13)
Grocott-Mason 2000	-	-	-	-
Grunkemeier 2012	16.21 (15.63-16.81)	-	-	-
Jamieson 2001	4.74 (4.20-5.36)	-	-	-
Jamieson 2006	4.77 (4.31-5.26)	-	0.86 (0.68-1.10)	-
Jamieson 2011	4.20 (3.72-4.74)	-	-	-
Johnston 2015	6.26 (6.10-6.43)[2]	-	-	-
Kurlansky 2007	9.54 (8.38-10.86)	-	-	-
Le Tourneau 2007	7.84 (6.63-9.26)	2.96 (2.24-3.91)	1.67 (1.15-2.42)	-
Lehmann 2011	5.87 (4.90-7.02)	2.04 (1.50-2.79)	0.52 (0.28-0.97)	-
Luciani 2001	2.44 (1.48-4.02)	1.30 (0.65-2.59)	0.33 (0.08-1.30)	0.08 (0.01-1.30)
McClure 2010	8.40 (7.72-9.13)	-	-	-
Merie 2012	9.21 (8.71-9.73)	7.00 (6.57-7.46)	-	-

Table S3. Continued

Author and publication year	Late mortality, %/y	Cardiac late mortality %/y	Valve-related late mortality, %/y	SUUD, %/y
Minakata 2014	5.72 (5.09-6.42)	1.55 (1.24-1.95)	0.72 (0.52-1.01)	-
Minami 2005	10.95 (10.31-11.64)	5.01 (4.56-5.50)	1.83 (1.57-2.14)	0.32 (0.22-0.47)
Mohammedi 2014	5.14 (4.59-5.77)	-	-	-
Myken 2009	5.96 (5.49-6.47)	3.17 (2.82-3.55)	0.52 (0.39-0.69)	0.01 (0.00-0.09)
Pavoni 2007	6.39 (5.04-8.10)	3.09 (2.19-4.37)	0.50 (0.21-1.20)	-
Polvani 2005	2.43 (1.50-3.94)	0.91 (0.41-2.02)	0.61 (0.23-1.61)	0.08 (0.00-1.21)
Rizzoli 2006	5.39 (4.81-6.04)	3.25 (2.81-3.77)	2.16 (1.80-2.59)	0.35 (0.22-0.55)
Ruggieri 2012	9.88 (9.26-10.55)	2.30 (2.00-2.65)	1.11 (0.91-1.37)	-
Sakamoto 2006	-	-	-	-
Sansone 2014	5.52 (4.45-6.84)	3.14 (2.36-4.19)	2.17 (1.53-3.07)	0.03 (0.00-0.56)
Silberman 2008	3.62 (2.55-5.14)	-	-	-
Sjögren 2006	13.21 (11.22-15.56)	9.62 (7.91-11.69)	2.43 (1.62-3.64)	0.05 (0.00-0.84)
Stanger 2014	5.58 (4.21-7.38)	-	-	-
Pooled total	**5.70 (4.99-6.53)**	**2.49 (1.95-3.18)**	**0.92 (0.74-1.15)**	**0.15 (0.09-0.26)**
I^2, % (χ2 P-value)	**99 (0.000)**	**98 (0.000)**	**94 (0.000)**	**90 (0.000)**

95% confidence intervals provided in parentheses. SUUD: sudden unexpected unexplained death. "-": variable not reported. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event. 1Including early deaths. 2Number of patients that died before valve explant.

Table S4. Pooled estimates of late mortality after AVR with allografts.

Author and publication year	Late mortality, %/y	Cardiac late mortality %/y	Valve-related late mortality, %/y	SUUD, %/y
Ali 2010	-	-	-	-
Ganguly 2004	2.26 (1.23-4.18)	1.13 (0.47-2.70)	0.23 (0.03-1.60)	-
Grocott-Mason 2000	-	-	0.70 (0.47-1.02)	-
Hickey 2007	2.56 (2.06-3.17)	1.30 (0.96-1.76)	-	-
Kaya 2005	1.79 (1.16-2.76)	0.81 (0.42-1.54)	0.45 (0.19-1.07)	-
Killian 2010	0.73 (0.54-1.00)	-	0.21 (0.11-0.37)	-
Kitamura 2011	1.52 (0.69-3.36)	1.01 (0.38-2.69)	0.25 (0.04-1.79)	-
Mokhles 2014	2.06 (1.65-2.56)	1.02 (0.74-1.39)	0.60 (0.40-0.90)	0.39 (0.24-0.65)
O'Brien 2001	2.59 (2.26-2.98)	0.94 (0.74-1.18)	0.37 (0.26-0.54)	-
Ruzmetov 2012	1.54 (0.64-3.66)	0.92 (0.30-2.84)	0.15 (0.01-2.45)	0.15 (0.01-2.45)
Smedira 2006	-	-	-	-
Talwar 2005	0.54 (0.20-1.44)	-	0.27 (0.07-1.08)	-
Vuran 2012	1.79 (0.68-4.73)	0.45 (0.06-3.16)	-	-
Wasywich 2003	-	-	-	-
Pooled total	**1.68 (1.23-2.28)**	**1.03 (0.88-1.19)**	**0.41 (0.29-0.58)**	**0.38 (0.23-0.62)**
I^2, % (χ2 P-value)	**86 (0.000)**	**0 (0.760)**	**51 (0.037)**	**0 (0.516)**

95% confidence intervals provided in parentheses. SUUD: sudden unexpected unexplained death. "-": variable not reported. *≤1 study reported this outcome measure. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event.

Table S5. Pooled estimates of late valve-related events after AVR with bioprostheses.

Author and publication year	SVD, %/y	NSVD, %/y	Valve thrombosis, %/y	Thromboembolism, %/y	Bleeding, %/y	Endocarditis, %/y
Akins 2002	0.17 (0.06-0.45)	0.02 (0.00-0.34)	-	1.35 (0.95-1.90)	0.55 (0.32-0.94)	0.17 (0.06-0.45)
Albert 2010	-	-	-	-	-	-
Amabile 2014	0.61 (0.38-0.96)	-	0.02 (0.00-0.27)	0.84 (0.57-1.24)	0.94 (0.65-1.36)	0.47 (0.28-0.79)
Anselmi 2014	0.32 (0.22-0.47)	0.10 (0.05-0.20)	0.05 (0.02-0.13)	0.81 (0.64-1.03)	-	0.18 (0.11-0.31)
Ashikhmina 2011	0.48 (0.38-0.61)	-	-	-	-	-
Benetis 2014	-	-	-	-	0.24 (0.06-0.96)	0.48 (0.18-1.27)
Benhameid 2008	1.81 (1.23-2.67)	-	-	-	-	-
Biglioli 2004	-	-	-	1.12 (0.72-1.73)	0.28 (0.12-0.67)	0.34 (0.15-0.75)
Birla 2013	0.08 (0.02-0.33)	0.17 (0.06-0.44)	0.02 (0.00-0.33)	1.61 (1.18-2.20)	-	0.21 (0.09-0.50)
Bottio 2004	0.25 (0.08-0.76)	0.58 (0.28-1.21)	0.08 (0.01-0.58)	0.91 (0.50-1.63)	0.49 (0.22-1.10)	0.16 (0.04-0.66)
Bottio 2005	-	0.63 (0.38-1.05)	-	0.72 (0.45-1.15)	0.68 (0.41-1.10)	0.46 (0.26-0.84)
Bourguignon 2015	0.85 (0.73-0.99)	0.07 (0.04-0.12)	0.00 (0.00-0.04)	0.72 (0.61-0.85)	0.34 (0.26-0.43)	0.38 (0.30-0.48)
Celiento 2012	0.20 (0.05-0.79)	-	0.05 (0.00-0.79)	0.59 (0.27-1.31)	0.30 (0.10-0.91)	0.39 (0.15-1.05)
Chan 2006	-	-	-	-	-	-
Chan 2011	-	-	-	-	-	-
Chiang 2014	-	-	-	-	0.37 (0.29-0.48)	-
David 2008	1.79 (1.36-2.36)	-	-	1.28 (0.92-1.78)	0.04 (0.01-0.26)	0.44 (0.25-0.77)
David 2010	0.62 (0.50-0.76)	0.03 (0.01-0.08)	0.00 (0.00-0.06)	0.88 (0.74-1.05)	0.30 (0.22-0.40)	0.29 (0.21-0.40)
de la Fuente 2003	0.16 (0.04-0.64)	0.08 (0.01-0.57)	0.04 (0.00-0.64)	0.32 (0.12-0.86)	0.16 (0.04-0.64)	0.31 (0.12-0.84)
Dellgren 2002a	0.33 (0.12-0.88)	-	-	1.40 (0.87-2.25)	0.08 (0.01-0.58)	0.41 (0.17-0.99)
Dellgren 2002b	0.36 (0.09-1.42)	-	-	2.85 (1.76-4.61)	-	0.18 (0.03-1.26)
Desai 2004	1.04 (0.59-1.82)	-	0.09 (0.01-0.61)	0.52 (0.23-1.15)	-	0.43 (0.18-1.04)
Eichinger 2008	0.69 (0.46-1.04)	0.30 (0.16-0.56)	-	2.11 (1.67-2.66)	0.84 (0.58-1.22)	0.54 (0.34-0.86)
Flameng 2014	1.50 (1.20-1.89)	-	-	-	-	0.41 (0.27-0.64)
Forcillo 2013	0.44 (0.34-0.56)	-	-	0.55 (0.45-0.69)	-	-
Franzen 2001	0.12 (0.01-1.94)	0.73 (0.24-2.25)	0.12 (0.01-1.94)	2.91 (1.67-5.09)	0.73 (0.24-2.25)	0.12 (0.01-1.94)
Frapier 2002	-	-	-	-	-	-
Gansera 2014	0.12 (0.03-0.48)	0.12 (0.03-0.48)	0.06 (0.01-0.43)	1.45 (0.97-2.16)	0.06 (0.01-0.43)	0.06 (0.01-0.43)

Table S5. Continued

Author and publication year	SVD, %/y	NSVD, %/y	Valve thrombosis, %/y	Thromboembolism, %/y	Bleeding, %/y	Endocarditis, %/y
Glaser 2014	0.01 (0.00-0.13)	0.01 (0.00-0.13)	0.01 (0.00-0.13)	0.01 (0.00-0.13)	0.01 (0.00-0.13)	0.01 (0.00-0.13)
Grocott-Mason 2000	1.23 (0.40-3.78)	-	-	1.23 (0.40-3.78)	0.82 (0.21-3.25)	1.23 (0.40-3.78)
Grunkemeier 2012	0.25 (0.18-0.35)	-	-	-	-	-
Jamieson 2001	0.42 (0.28-0.64)	0.77 (0.56-1.05)	-	2.44 (2.05-2.90)	0.83 (0.61-1.11)	0.69 (0.50-0.96)
Jamieson 2006	-	-	-	-	-	-
Jamieson 2011	-	-	-	-	-	-
Johnston 2015	-	-	-	-	-	-
Kurlansky 2007	-	-	-	-	-	-
Le Tourneau 2007	1.11 (0.70-1.76)	-	-	1.79 (1.25-2.57)	0.86 (0.51-1.46)	0.49 (0.25-0.99)
Lehmann 2011	0.16 (0.05-0.49)	0.16 (0.05-0.49)	-	1.62 (1.15-2.30)	0.05 (0.01-0.37)	0.21 (0.08-0.56)
Luciani 2001	0.65 (0.24-1.73)	0.33 (0.08-1.30)	-	0.33 (0.08-1.30)	0.65 (0.24-1.73)	-
McClure 2010	0.22 (0.13-0.37)	0.03 (0.01-0.13)	-	0.38 (0.26-0.58)	0.30 (0.19-0.48)	0.27 (0.16-0.44)
Merie 2012	-	-	-	4.90 (4.53-5.29)	2.90 (2.62-3.21)	-
Minakata 2014	0.38 (0.24-0.61)	0.02 (0.00-0.15)	-	0.81 (0.59-1.11)	1.02 (0.77-1.35)	0.17 (0.09-0.34)
Minami 2005	1.00 (0.81-1.24)	0.34 (0.24-0.50)	-	0.81 (0.64-1.02)	0.31 (0.21-0.45)	0.62 (0.47-0.81)
Mohammedi 2014	-	-	-	-	-	-
Myken 2009	0.88 (0.71-1.10)	-	-	1.57 (1.33-1.85)	0.87 (0.70-1.09)	0.27 (0.18-0.40)
Pavoni 2007	3.29 (2.35-4.61)	1.10 (0.61-1.98)	-	1.30 (0.76-2.23)	0.60 (0.27-1.33)	0.70 (0.33-1.46)
Polvani 2005	0.76 (0.32-1.82)	-	-	0.76 (0.32-1.82)	0.08 (0.00-1.21)	0.15 (0.02-1.08)
Rizzoli 2006	0.40 (0.26-0.62)	-	0.06 (0.02-0.18)	1.29 (1.02-1.64)	0.48 (0.33-0.71)	0.44 (0.29-0.67)
Ruggieri 2012	0.71 (0.55-0.92)	0.31 (0.21-0.45)	-	1.13 (0.92-1.38)	-	0.24 (0.16-0.38)
Sakamoto 2006	-	-	-	0.27 (0.04-1.88)	-	0.53 (0.13-2.12)
Sansone 2014	3.28 (2.48-4.35)	-	-	-	-	-
Silberman 2008	0.24 (0.06-0.96)	-	0.06 (0.00-0.96)	0.12 (0.02-0.86)	0.12 (0.02-0.86)	0.72 (0.33-1.61)
Sjögren 2006	1.16 (0.65-2.09)	0.05 (0.00-0.84)	-	3.59 (2.58-5.00)	0.63 (0.29-1.41)	0.74 (0.35-1.55)
Stanger 2014	-	-	-	-	-	-
Pooled total	**0.60 (0.47-0.76)**	**0.20 (0.13-0.32)**	**0.04 (0.03-0.07)**	**1.10 (0.83-1.47)**	**0.44 (0.30-0.65)**	**0.38 (0.32-0.44)**
I^2, % ($\chi 2$ P-value)	**93 (0.000)**	**88 (0.000)**	**0 (0.651)**	**97 (0.000)**	**96 (0.000)**	**57 (0.000)**

95% confidence intervals provided in parentheses. SVD: structural valve deterioration. NSVD: non-structural dysfunction. "-": variable not reported. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event.

Table S6. Pooled estimates of late valve-related events after AVR with allografts.

Author and publication year	SVD, %/y	NSVD, %/y	Valve thrombosis, %/y	Thromboembolism, %/y	Bleeding, %/y	Endocarditis, %/y
Ali 2010	-	-	-	-	-	-
Ganguly 2004	2.49 (1.39-4.46)	-	-	-	-	-
Grocott-Mason 2000	3.91 (3.34-4.58)	0.01 (0.00-0.21)	-	1.66 (1.30-2.13)	0.19 (0.09-0.39)	0.48 (0.30-0.76)
Hickey 2007	-	-	-	-	-	0.19 (0.09-0.42)
Kaya 2005	1.07 (0.61-1.88)	-	-	0.09 (0.01-0.63)	0.04 (0.00-0.71)	0.36 (0.13-0.95)
Killian 2010	-	-	-	0.24 (0.14-0.42)	0.13 (0.06-0.28)	-
Kitamura 2011	-	-	-	-	-	-
Mokhles 2014	-	-	-	-	-	-
O'Brien 2001	-	-	-	0.74 (0.57-0.96)	-	0.45 (0.33-0.64)
Ruzmetov 2012	-	-	-	-	-	-
Smedira 2006	-	-	-	-	-	-
Talwar 2005	-	-	-	0.07 (0.00-1.08)	-	0.68 (0.28-1.62)
Vuran 2012	-	-	-	-	-	-
Wasywich 2003	-	-	-	-	-	-
Pooled total	**2.26 (1.02-4.97)**	*	*	**0.46 (0.20-1.08)**	**0.15 (0.09-0.25)**	**0.42 (0.31-0.58)**
I^2, % ($\chi 2$ P-value)	**90 (0.000)**			**93 (0.000)**	**0 (0.548)**	**28 (0.236)**

95% confidence intervals provided in parentheses. SVD: structural valve deterioration. NSVD: non-structural dysfunction. "-": variable not reported. *≤1 study reported this outcome measure. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event.

Table S7. Pooled estimates of re-intervention after AVR with bioprostheses.

	Re-interventions					
Author and publication year	**Total, %/y**	**Valve-related, %/y**	**SVD, %/y**	**NSVD, %/y**	**Valve thrombosis, %/y**	**Endocarditis, %/y**
Akins 2002	0.42 (0.23-0.78)	0.34 (0.17-0.67)	0.17 (0.06-0.45)	0.02 (0.00-0.34)	0.02 (0.00-0.34)	0.17 (0.06-0.45)
Albert 2010	-	-	-	-	-	-
Amabile 2014	0.67 (0.43-1.04)	0.34 (0.18-0.62)	0.34 (0.18-0.62)	-	-	-
Anselmi 2014	0.14 (0.08-0.24)	0.14 (0.08-0.24)	0.10 (0.05-0.20)	0.01 (0.00-0.09)	-	0.02 (0.01-0.10)
Ashikhmina 2011	0.34 (0.25-0.45)	0.34 (0.25-0.45)	0.34 (0.25-0.45)	-	-	-
Benetis 2014	0.48 (0.18-1.27)	0.48 (0.18-1.27)	0.06 (0.00-0.96)	0.06 (0.00-0.96)	0.06 (0.00-0.96)	0.48 (0.18-1.27)
Benhameid 2008	1.88 (1.29-2.76)	1.88 (1.29-2.76)	-	-	-	-
Biglioli 2004	1.57 (1.09-2.27)	1.57 (1.09-2.27)	-	-	-	-
Birla 2013	0.17 (0.06-0.44)	0.17 (0.06-0.44)	0.04 (0.01-0.29)	0.04 (0.01-0.29)	0.02 (0.00-0.33)	0.04 (0.01-0.29)
Bottio 2004	0.66 (0.33-1.31)	0.66 (0.33-1.31)	0.08 (0.01-0.58)	0.49 (0.22-1.10)	0.04 (0.00-0.66)	0.04 (0.00-0.66)
Bottio 2005	4.05 (3.33-4.93)	-	-	-	-	-
Bourguignon 2015	0.91 (0.78-1.06)	0.91 (0.78-1.06)	0.67 (0.56-0.79)	0.05 (0.03-0.09)	0.00 (0.00-0.04)	0.12 (0.08-0.19)
Celiento 2012	0.59 (0.27-1.31)	0.59 (0.27-1.31)	0.20 (0.05-0.79)	0.05 (0.00-0.79)	0.05 (0.00-0.79)	0.39 (0.15-1.05)
Chan 2006	1.33 (1.16-1.51)	1.33 (1.16-1.51)	0.88 (0.75-1.04)	0.24 (0.18-0.33)	0.03 (0.01-0.07)	0.17 (0.12-0.25)
Chan 2011	1.61 (1.44-1.80)	1.61 (1.44-1.80)	-	-	-	-
Chiang 2014	0.51 (0.41-0.63)	0.51 (0.41-0.63)	-	-	-	-
David 2008	1.83 (1.39-2.41)	1.83 (1.39-2.41)	1.65 (1.23-2.20)	0.02 (0.00-0.29)	0.02 (0.00-0.29)	0.18 (0.08-0.44)
David 2010	0.74 (0.61-0.90)	0.74 (0.61-0.90)	0.53 (0.42-0.66)	0.02 (0.01-0.07)	0.00 (0.00-0.06)	0.11 (0.07-0.19)
de la Fuente 2003	0.56 (0.27-1.18)	0.56 (0.27-1.18)	0.16 (0.04-0.64)	0.08 (0.01-0.57)	0.04 (0.00-0.64)	0.32 (0.12-0.86)
Dellgren 2002a	0.49 (0.22-1.10)	0.49 (0.22-1.10)	0.33 (0.12-0.88)	0.04 (0.00-0.66)	0.04 (0.00-0.66)	0.16 (0.04-0.66)
Dellgren 2002b	0.53 (0.17-1.65)	0.53 (0.17-1.65)	0.36 (0.09-1.42)	0.09 (0.01-1.42)	0.09 (0.01-1.42)	0.18 (0.03-1.26)
Desai 2004	1.04 (0.59-1.82)	1.04 (0.59-1.82)	0.78 (0.41-1.49)	0.04 (0.00-0.69)	0.04 (0.00-0.69)	0.26 (0.08-0.80)
Eichinger 2008	0.96 (0.68-1.36)	0.96 (0.68-1.36)	0.48 (0.30-0.79)	0.12 (0.05-0.32)	0.03 (0.00-0.21)	0.21 (0.10-0.44)

Table S7. Continued

	Re-interventions					
Author and publication year	**Total, %/y**	**Valve-related, %/y**	**SVD, %/y**	**NSVD, %/y**	**Valve thrombosis, %/y**	**Endocarditis, %/y**
Flameng 2014	-	-	-	-	-	-
Forcillo 2013	0.62 (0.50-0.76)	0.62 (0.50-0.76)	-	-	-	-
Franzen 2001	0.24 (0.03-1.72)	0.24 (0.03-1.72)	0.12 (0.01-1.94)	0.24 (0.03-1.72)	0.12 (0.01-1.94)	0.12 (0.01-1.94)
Frapier 2002	-	-	-	-	-	-
Gansera 2014	0.36 (0.16-0.81)	0.36 (0.16-0.81)	0.12 (0.03-0.48)	0.12 (0.03-0.48)	0.06 (0.01-0.43)	0.06 (0.01-0.43)
Glaser 2014	0.35 (0.23-0.53)	0.35 (0.23-0.53)	0.18 (0.10-0.33)	0.03 (0.01-0.13)	0.01 (0.00-0.13)	0.10 (0.04-0.22)
Grocott-Mason 2000	-	-	-	-	-	-
Grunkemeier 2012	-	-	-	-	-	-
Jamieson 2001	1.09 (0.85-1.42)	1.09 (0.85-1.42)	-	-	-	-
Jamieson 2006	0.63 (0.48-0.83)	0.63 (0.48-0.84)	-	-	-	-
Jamieson 2011	1.11 (0.88-1.41)	1.11 (0.88-1.41)	0.47 (0.32-0.67)	0.20 (0.11-0.35)	0.07 (0.02-0.18)	0.33 (0.21-0.52)
Johnston 2015	0.43 (0.39-0.48)	0.43 (0.39-0.48)	0.19 (0.16-0.22)	-	0.00 (0.00-0.01)	0.18 (0.15-0.21)
Kurlansky 2007	0.05 (0.01-0.33)	-	-	-	-	-
Le Tourneau 2007	-	-	-	-	-	-
Lehmann 2011	0.47 (0.25-0.90)	0.47 (0.25-0.90)	0.16 (0.05-0.49)	0.16 (0.05-0.49)	0.03 (0.00-0.42)	0.16 (0.05-0.49)
Luciani 2001	0.81 (0.34-1.95)	0.81 (0.34-1.95)	0.65 (0.24-1.73)	0.16 (0.02-1.15)	0.08 (0.01-1.30)	0.08 (0.01-1.30)
McClure 2010	0.65 (0.48-0.89)	0.55 (0.39-0.77)	0.22 (0.13-0.37)	0.03 (0.01-0.13)	0.01 (0.00-0.13)	0.18 (0.10-0.33)
Merie 2012	-	-	-	-	-	-
Minakata 2014	0.51 (0.34-0.76)	0.49 (0.33-0.73)	0.38 (0.24-0.61)	0.02 (0.00-0.15)	0.01 (0.00-0.17)	0.08 (0.03-0.23)
Minami 2005	1.20 (0.99-1.46)	1.20 (0.99-1.46)	0.94 (0.75-1.17)	-	-	-
Mohammedi 2014	1.25 (0.98-1.58)	1.25 (0.98-1.58)	0.71 (0.52-0.98)	0.38 (0.25-0.59)	0.01 (0.00-0.15)	0.15 (0.07-0.29)
Myken 2009	1.15 (0.95-1.40)	1.15 (0.95-1.40)	0.88 (0.71-1.10)	-	-	0.27 (0.18-0.40)
Pavoni 2007	2.89 (2.02-4.14)	2.89 (2.02-4.14)	1.70 (1.06-2.72)	0.60 (0.27-1.33)	0.05 (0.00-0.80)	0.60 (0.27-1.33)
Polvani 2005	0.76 (0.32-1.82)	0.76 (0.32-1.82)	0.76 (0.32-1.82)	-	-	-

Table S7. Continued

	Re-interventions					
Author and publication year	**Total, %/y**	**Valve-related, %/y**	**SVD, %/y**	**NSVD, %/y**	**Valve thrombosis, %/y**	**Endocarditis, %/y**
Rizzoli 2006	0.73 (0.53-1.00)	0.71 (0.52-0.98)	0.37 (0.23-0.57)	-	0.04 (0.01-0.15)	0.23 (0.13-0.41)
Ruggieri 2012	0.43 (0.31-0.60)	0.43 (0.31-0.60)	0.43 (0.31-0.60)	-	-	-
Sakamoto 2006	0.27 (0.04-1.88)	0.27 (0.04-1.88)	-	-	-	-
Sansone 2014	1.40 (0.90-2.16)	1.40 (0.90-2.16)	1.12 (0.69-1.82)	0.07 (0.01-0.50)	-	0.21 (0.07-0.65)
Silberman 2008	0.60 (0.25-1.45)	0.60 (0.25-1.45)	0.24 (0.06-0.96)	-	-	0.36 (0.12-1.12)
Sjögren 2006	0.21 (0.05-0.84)	0.21 (0.05-0.84)	0.11 (0.01-0.75)	0.05 (0.00-0.84)	-	0.11 (0.01-0.75)
Stanger 2014	1.70 (1.01-2.85)	1.70 (1.01-2.85)	1.09 (0.57-2.09)	0.61 (0.25-1.45)	-	-
Pooled total	**0.75 (0.61-0.91)**	**0.72 (0.60-0.86)**	**0.42 (0.33-0.54)**	**0.11 (0.07-0.17)**	**0.03 (0.02-0.05)**	**0.19 (0.16-0.23)**
I^2, % (χ2 P-value)	**95 (0.000)**	**94 (0.000)**	**92 (0.000)**	**74 (0.000)**	**0 (0.642)**	**46 (0.004)**

95% confidence intervals provided in parentheses. SVD: structural valve deterioration. NSVD: non-structural dysfunction. "-": variable not reported. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event.

Table S8. Pooled estimates of re-intervention after AVR with allografts.

	Re-interventions					
Author and publication year	**Total, %/y**	**Valve-related, %/y**	**SVD, %/y**	**NSVD, %/y**	**Valve thrombosis, %/y**	**Endocarditis, %/y**
Ali 2010	-	-	-	-	-	-
Ganguly 2004	2.49 (1.39-4.46)	2.49 (1.39-4.46)	-	-	-	0.11 (0.01-1.81)
Grocott-Mason 2000	1.98 (1.58-2.48)	1.98 (1.58-2.48)	1.85 (1.46-2.33)	0.01 (0.00-0.21)	0.01 (0.00-0.21)	0.13 (0.06-0.32)
Hickey 2007	2.47 (1.98-3.07)	2.47 (1.98-3.07)	-	-	-	-
Kaya 2005	1.88 (1.23-2.87)	1.61 (1.02-2.55)	1.07 (0.61-1.88)	0.04 (0.00-0.71)	0.04 (0.00-0.71)	0.27 (0.09-0.83)
Killian 2010	1.16 (0.91-1.49)	1.16 (0.91-1.49)	0.45 (0.30-0.67)	0.34 (0.21-0.54)	0.01 (0.00-0.15)	0.38 (0.24-0.58)
Kitamura 2011	2.03 (1.02-4.02)	2.03 (1.02-4.02)	2.03 (1.02-4.02)	-	-	-
Mokhles 2014	2.68 (2.22-3.24)	2.68 (2.22-3.24)	2.11 (1.70-2.62)	0.47 (0.30-0.74)	0.01 (0.00-0.21)	0.10 (0.04-0.28)
O'Brien 2001	1.81 (1.53-2.13)	1.81 (1.53-2.13)	1.22 (0.99-1.49)	0.01 (0.00-0.11)	0.01 (0.00-0.11)	0.28 (0.18-0.43)
Ruzmetov 2012	4.30 (2.58-7.18)	4.30 (2.58-7.18)	-	-	-	-
Smedira 2006	1.18 (0.89-1.58)	1.18 (0.89-1.58)	0.69 (0.48-1.01)	0.01 (0.00-0.21)	0.01 (0.00-0.21)	0.44 (0.27-0.70)
Talwar 2005	0.81 (0.37-1.80)	0.68 (0.28-1.62)	-	-	0.07 (0.00-1.08)	0.14 (0.02-0.96)
Vuran 2012	0.90 (0.23-3.56)	0.90 (0.23-3.56)	0.22 (0.01-3.57)	0.22 (0.01-3.57)	0.22 (0.01-3.57)	0.45 (0.06-3.16)
Wasywich 2003	1.70 (0.77-3.75)	1.70 (0.77-3.75)	-	-	-	-
Pooled total	**1.87 (1.52-2.31)**	**1.85 (1.49-2.29)**	**1.15 (0.77-1.70)**	**0.13 (0.05-0.32)**	**0.02 (0.01-0.06)**	**0.27 (0.19-0.38)**
I^2, % ($\chi 2$ P-value)	**80 (0.000)**	**81 (0.000)**	**90 (0.000)**	**73 (0.001)**	**0 (0.655)**	**36 (0.128)**

95% confidence intervals provided in parentheses. SVD: structural valve deterioration. NSVD: non-structural valve dysfunction. "-": variable not reported. In case an event was reported not to occur, for pooling purposes it was assumed that 0.5 patient experienced the event.

Results univariate meta-regression analyses

Table S9. Univariate meta-regression early mortality.

	Bioprostheses					Allografts				
	B	**CI -**	**CI +**	**S.E.**	**p-value**	**B**	**CI -**	**CI +**	**S.E.**	**p-value**
Implantation period start (year)	-0.015	0.032	0.003	0.009	0.102	0.028	0.008	0.048	0.010	0.005*
Implantation period end (year)	-0.030	-0.047	-0.014	0.008	<0.001*	0.036	-0.020	0.092	0.029	0.212
Prospective vs. retrospective study design	-0.054	-0.307	0.199	0.129	0.676	-0.519	-1.386	0.349	0.443	0.241
Mean age, y	-0.005	-0.028	0.018	0.012	0.663	0.002	-0.028	0.032	0.015	0.902
Male (%)	-1.057	-2.035	-0.080	0.499	0.034*	1.462	-2.531	5.454	2.037	0.473
Concomitant procedures (%)	-0.004	-0.009	0.002	0.003	0.197	-0.082	-0.135	-0.028	0.027	0.003*
Concomitant CABG (%)	-0.373	1.017	0.271	0.329	0.256	4.651	-3.360	12.663	4.088	0.255
Pre-NYHA III/IV (%)	0.103	-0.504	0.710	0.310	0.740	1.747	-0.471	3.964	1.131	0.123
Stentless vs. stented valves	-0.252	-0.594	0.090	0.175	0.149	n/a	n/a	n/a	n/a	n/a
Pericardial vs. porcine valves	-0.004	-0.308	0.299	0.155	0.978	n/a	n/a	n/a	n/a	n/a
Subcoronary valve replacement (%)	n/a	n/a	n/a	n/a	n/a	0.037	-1.085	1.158	0.572	0.949
Endocarditis (indication for surgery)	n/a	n/a	n/a	n/a	n/a	1.539	-1.563	4.640	4.582	0.331

B: beta coefficient. CI: confidence interval. S.E.: standard error. CABG: coronary artery bypass grafting. NYHA: New York Heart Association. n/a is not applicable. *p-value<0.05.

Table S10. Univariate meta-regression late mortality.

	Bioprostheses					Allografts				
	B	**CI -**	**CI +**	**S.E.**	**p-value**	**B**	**CI -**	**CI +**	**S.E.**	**p-value**
Implantation period start (year)	-0.010	-0.026	0.006	0.008	0.233	-0.037	-0.061	-0.013	0.012	0.002*
Implantation period end (year)	-0.003	-0.023	0.017	0.010	0.772	-0.010	-0.022	0.001	0.006	0.081
Mean follow-up, y	-0.031	-0.087	0.028	0.029	0.283	-0.013	-0.088	0.063	0.039	0.746
Prospective vs. retrospective study design	0.102	-0.159	0.363	0.133	0.443	-0.568	-1.131	-0.005	0.287	0.048*
Mean age, y	0.044	0.024	0.063	0.010	<0.001*	0.011	-0.019	0.041	0.015	0.471
Male (%)	-0.988	-2.031	0.054	0.532	0.063	-0.028	-3.174	3.118	1.605	0.986
Concomitant procedures (%)	0.005	-0.001	0.011	0.003	0.086	-0.012	-0.047	0.023	0.018	0.505
Concomitant CABG (%)	0.652	0.006	1.298	0.330	0.048*	-1.739	-8.404	4.926	3.401	0.609
Pre-NYHA III/IV (%)	-0.043	-0.608	0.522	0.288	0.881	-1.932	-3.786	-0.078	0.946	0.041*
Stentless vs. stented valves	-0.298	-0.593	-0.003	0.151	0.048*	n/a	n/a	n/a	n/a	n/a
Pericardial vs. porcine valves	0.217	-0.022	0.455	0.122	0.076	n/a	n/a	n/a	n/a	n/a
Subcoronary valve replacement (%)	n/a	n/a	n/a	n/a	n/a	0.470	-0.296	1.236	0.391	0.229
Endocarditis (indication for surgery)	n/a	n/a	n/a	n/a	n/a	0.312	-1.489	2.114	0.919	0.734

B: beta coefficient. CI: confidence interval. S.E.: standard error. CABG: coronary artery bypass grafting. NYHA: New York Heart Association. n/a: not applicable. *p-value<0.05.

Table S11. Univariate meta-regression structural valve deterioration.

	Bioprostheses					Allografts				
	B	**CI -**	**CI +**	**S.E.**	**p-value**	**B**	**CI -**	**CI +**	**S.E.**	**p-value**
Implantation period start (year)	-0.007	-0.051	0.038	0.023	0.760	-0.043	-0.064	-0.021	0.011	<0.001*
Implantation period end (year)	-0.027	-0.079	0.025	0.027	0.312	-0.123	-0.177	-0.069	0.028	<0.001*
Mean follow-up, y	0.109	-0.017	0.235	0.064	0.091	0.210	0.105	0.315	0.054	<0.001*
Prospective vs. retrospective study design	-0.598	-1.175	-0.021	0.295	0.042*	0.109	-1.239	1.458	0.688	0.874
Mean age, y	-0.084	0.148	-0.020	0.033	0.010*	0.034	-0.091	0.159	0.064	0.596
Male (%)	-0.362	-2.760	2.036	1.223	0.767	3.379	-9.097	15.856	6.366	0.596
Concomitant procedures (%)	-0.004	-0.017	0.010	0.007	0.576	-	-	-	-	-
Concomitant CABG (%)	0.038	-1.333	1.408	0.699	0.957	7.871	-1.752	17.495	4.910	0.109
Pre-NYHA III/IV (%)	-0.119	-1.665	1.427	0.789	0.880	2.159	1.126	3.192	0.527	<0.001*
Stentless vs. stented valves	0.869	0.288	1.451	0.297	0.003*	n/a	n/a	n/a	n/a	n/a
Pericardial vs. porcine valves	0.021	-0.545	0.588	0.289	0.941	n/a	n/a	n/a	n/a	n/a
Subcoronary valve replacement (%)	n/a	n/a	n/a	n/a	n/a	1.413	0.778	2.049	0.324	<0.001*
Endocarditis (indication for surgery)	n/a	n/a	n/a	n/a	n/a	-	-	-	-	-

B: beta coefficient. CI: confidence interval. S.E.: standard error. CABG: coronary artery bypass grafting. NYHA: New York Heart Association. n/a is not applicable. *p-value<0.05.

Table S12. Univariate meta-regression non-structural valve dysfunction.

	Bioprostheses				
	B	**CI -**	**CI +**	**S.E.**	**p-value**
Implantation period start (year)	-0.009	-0.084	0.066	0.038	0.814
Implantation period end (year)	-0.078	-0.155	-0.001	0.039	0.047*
Mean follow-up, y	-0.056	-0.243	0.130	0.095	0.552
Prospective vs. retrospective study design	-0.542	1.546	0.462	0.512	0.290
Mean age, y	-0.033	-0.108	0.042	0.038	0.387
Male (%)	-5.082	-8.440	-1.723	1.713	0.003*
Concomitant procedures (%)	-0.018	-0.036	0.001	0.009	0.063
Concomitant CABG (%)	-1.686	-4.018	0.646	1.190	0.156
Pre-NYHA III/IV (%)	1.250	-1.243	3.744	1.272	0.326
Stentless vs. stented valves	1.343	-0.255	2.942	0.816	0.100
Pericardial vs. porcine valves	-0.698	1.795	0.398	0.560	0.212
Subcoronary valve replacement (%)	n/a	n/a	n/a	n/a	n/a

B: beta coefficient. CI: confidence interval. S.E.: standard error. CABG: coronary artery bypass grafting. NYHA: New York Heart Association. n/a is not applicable. *p-value<0.05.

Table S13. Univariate meta-regression thromboembolism.

	Bioprostheses					Allografts				
	B	**CI -**	**CI +**	**S.E.**	**p-value**	**B**	**CI -**	**CI +**	**S.E.**	**p-value**
Implantation period start (year)	-0.006	-0.045	0.034	0.020	0.780	-0.076	-0.116	-0.036	0.020	<0.001*
Implantation period end (year)	-0.018	-0.064	0.028	0.023	0.438	-0.182	-0.250	-0.114	0.035	<0.001*
Mean follow-up, y	-0.014	-0.142	0.113	0.065	0.826	0.032	-0.240	0.304	0.139	0.817
Prospective vs. retrospective study design	-0.446	1.068	0.176	0.318	0.160	-1.051	-2.537	0.434	0.758	0.165
Mean age, y	0.012	-0.033	0.057	0.023	0.601	0.084	-0.051	0.220	0.069	0.224
Male (%)	-0.258	-2.416	1.900	1.101	0.815	4.052	-27.896	36.001	16.300	0.804
Concomitant procedures (%)	0.004	-0.008	0.015	0.006	0.538	-	-	-	-	-
Concomitant CABG (%)	0.476	-0.794	1.747	0.648	0.463	29.071	4.174	53.968	12.703	0.022*
Pre-NYHA III/IV (%)	-0.217	-1.329	0.895	0.567	0.702	7.240	2.802	11.678	2.264	0.001*
Stentless vs. stented valves	0.060	-0.549	0.669	0.311	0.846	n/a	n/a	n/a	n/a	n/a
Pericardial vs. porcine valves	-0.229	-0.709	0.252	0.245	0.351	n/a	n/a	n/a	n/a	n/a
Subcoronary valve replacement (%)	n/a	n/a	n/a	n/a	n/a	2.824	2.061	3.586	0.389	<0.001*
Endocarditis (indication for surgery)	n/a	n/a	n/a	n/a	n/a	-1.612	-6.339	3.115	2.412	0.504

B: beta coefficient. CI: confidence interval. S.E.: standard error. CABG: coronary artery bypass grafting. NYHA: New York Heart Association. n/a is not applicable.

Table S14. Univariate meta-regression bleeding.

	Bioprostheses				
	B	**CI -**	**CI +**	**S.E.**	**p-value**
Implantation period start (year)	-0.006	-0.045	0.034	0.020	0.780
Implantation period end (year)	-0.018	-0.064	0.028	0.023	0.438
Mean follow-up, y	-0.014	-0.142	0.113	0.065	0.826
Prospective vs. retrospective study design	-0.446	1.068	0.176	0.318	0.160
Mean age, y	0.012	-0.033	0.057	0.023	0.601
Male (%)	-0.258	2.416	1.900	1.101	0.815
Concomitant procedures (%)	0.004	-0.008	0.015	0.006	0.538
Concomitant CABG (%)	0.476	-0.794	1.747	0.648	0.463
Pre-NYHA III/IV (%)	-0.217	-1.329	0.895	0.567	0.702
Stentless vs. stented valves	0.060	-0.549	0.669	0.311	0.846
Pericardial vs. porcine valves	-0.229	-0.709	-0.252	-0.245	0.351
Subcoronary valve replacement (%)	n/a	n/a	n/a	n/a	n/a

B: beta coefficient. CI: confidence interval. S.E.: standard error. CABG: coronary artery bypass grafting. NYHA: New York Heart Association. n/a is not applicable.

Table S15. Univariate meta-regression endocarditis.

	Bioprostheses				
	B	**CI -**	**CI +**	**S.E.**	**p-value**
Implantation period start (year)	-0.013	-0.038	0.012	0.013	0.303
Implantation period end (year)	-0.014	-0.042	0.014	0.014	0.339
Mean follow-up, y	-0.058	0.119	0.002	0.031	0.060
Prospective vs. retrospective study design	-0.298	0.629	0.034	0.169	0.078
Mean age, y	-0.014	-0.043	0.015	0.015	0.343
Male (%)	-0.654	-1.958	0.651	0.665	0.326
Concomitant procedures (%)	-0.003	-0.010	0.004	0.003	0.401
Concomitant CABG (%)	0.066	-0.776	0.908	0.429	0.878
Pre-NYHA III/IV (%)	0.403	-0.309	1.115	0.363	0.267
Stentless vs. stented valves	0.218	-0.234	0.671	0.231	0.345
Pericardial vs. porcine valves	-0.065	-0.435	0.305	0.189	0.730
Subcoronary valve replacement (%)	n/a	n/a	n/a	n/a	n/a

B: beta coefficient. CI: confidence interval. S.E.: standard error. CABG: coronary artery bypass grafting. NYHA: New York Heart Association. n/a is not applicable.

Table S16. Univariate meta-regression re-intervention.

	Bioprostheses					Allografts				
	B	**CI -**	**CI +**	**S.E.**	**p-value**	**B**	**CI -**	**CI +**	**S.E.**	**p-value**
Implantation period start (year)	-0.025	-0.052	0.002	0.014	0.074	-0.008	-0.032	0.015	0.012	0.489
Implantation period end (year)	-0.023	-0.055	0.010	0.017	0.170	0.007	-0.019	0.033	0.013	0.595
Mean follow-up, y	0.059	-0.030	0.149	0.046	0.194	0.016	-0.043	0.075	0.030	0.585
Prospective vs. retrospective study design	-0.250	-0.672	0.172	0.215	0.246	-0.447	-0.793	-0.101	0.177	0.011*
Mean age, y	-0.078	-0.109	0.048	0.016	<0.001*	-0.009	-0.027	0.010	0.009	0.361
Male (%)	-0.318	-2.109	1.472	0.914	0.727	-1.695	-3.514	0.125	0.928	0.068
Concomitant procedures (%)	-0.004	-0.013	0.004	0.004	0.318	0.006	-0.022	0.034	0.014	0.686
Concomitant CABG (%)	-0.135	-1.182	0.913	0.534	0.801	-1.808	-5.902	2.285	2.088	0.386
Pre-NYHA III/IV (%)	0.243	-0.954	1.440	0.611	0.691	-0.001	-1.137	1.134	0.579	0.998
Stentless vs. stented valves	0.512	0.007	1.018	0.258	0.047*	n/a	n/a	n/a	n/a	n/a
Pericardial vs. porcine valves	-0.176	-0.639	0.286	0.236	0.454	n/a	n/a	n/a	n/a	n/a
Subcoronary valve replacement (%)	n/a	n/a	n/a	n/a	n/a	0.180	-0.414	0.774	0.303	0.553
Endocarditis (indication for surgery)	n/a	n/a	n/a	n/a	n/a	-0.087	-1.813	1.638	0.880	0.921

B: beta coefficient. CI: confidence interval. S.E.: standard error. CABG: coronary artery bypass grafting. NYHA: New York Heart Association. n/a is not applicable.

Results subgroup analyses prospective versus retrospective studies

Table S17. Subgroup analysis prospective versus retrospective studies on bioprostheses.

BIOPROSTHESES	Prospective studies	Reported in n studies	Retrospective studies	Reported in n studies
Study characteristics				
No. of studies	16		38	
No. of patients	29,436		26,276	
Mean follow-up, y ±SD	6.7 ± 4.5	16	6.7 ± 4.9	38
Mean age, y ±SD	71.9 ± 10.0	15	71.6 ± 8.4	37
Male, %	64.1	13	57.8	35
Concomitant CABG, %	43.5	16	34.4	32
Early mortality, %				
Early mortality	4.63 (3.52-6.08)	14	5.22 (4.64-5.88)	34
Early valve-related events, %				
SVD	*	1	0.79 (0.03-22.36)	3
NSVD	*	1	0.18 (0.01-3.01)	2
Valve thrombosis	*	0	0.26 (0.10-0.68)	4
Thromboembolism	1.72 (0.32-9.17)	3	3.71 (2.26-6.10)	5
Reexploration for bleeding	3.17 (1.59-6.33)	6	4.30 (2.84-6.52)	9
Endocarditis	0.27 (0.03-2.05)	2	0.13 (0.03-0.60)	3
Late mortality, %/year				
Late mortality	6.12 (4.70-7.97)	15	5.53 (4.78-6.40)	32
Cardiac late mortality	2.20 (1.52-3.17)	9	2.53 (1.94-3.31)	21
Valve-related late mortality	0.82 (0.47-1.44)	9	0.95 (0.76-1.19)	25
SUUD	0.07 (0.01-0.73)	5	0.17 (0.10-0.28)	17
Late valve-related events, %/year				
SVD	0.43 (0.32-0.60)	11	0.66 (0.48-0.91)	27
NSVD	0.14 (0.06-0.31)	7	0.23 (0.13-0.40)	14
Valve thrombosis	0.02 (0.01-0.06)	6	0.05 (0.03-0.10)	8
Thromboembolism	1.09 (0.83-1.43)	9	1.06 (0.75-1.49)	28
Bleeding	0.36 (0.22-0.59)	7	0.45 (0.29-0.70)	25
Endocarditis	0.33 (0.28-0.38)	10	0.40 (0.32-0.50)	26
Re-interventions, %/year				
Total	0.63 (0.46-0.88)	15	0.81 (0.63-1.04)	32
Valve-related	0.61 (0.43-0.85)	15	0.79 (0.64-0.98)	30
SVD	0.34 (0.23-0.49)	14	0.50 (0.37-0.67)	23
NSVD	0.12 (0.06-0.25)	10	0.10 (0.05-0.17)	18
Valve thrombosis	0.02 (0.01-0.05)	11	0.03 (0.02-0.05)	15
Endocarditis	0.18 (0.13-0.24)	11	0.19 (0.15-0.25)	20

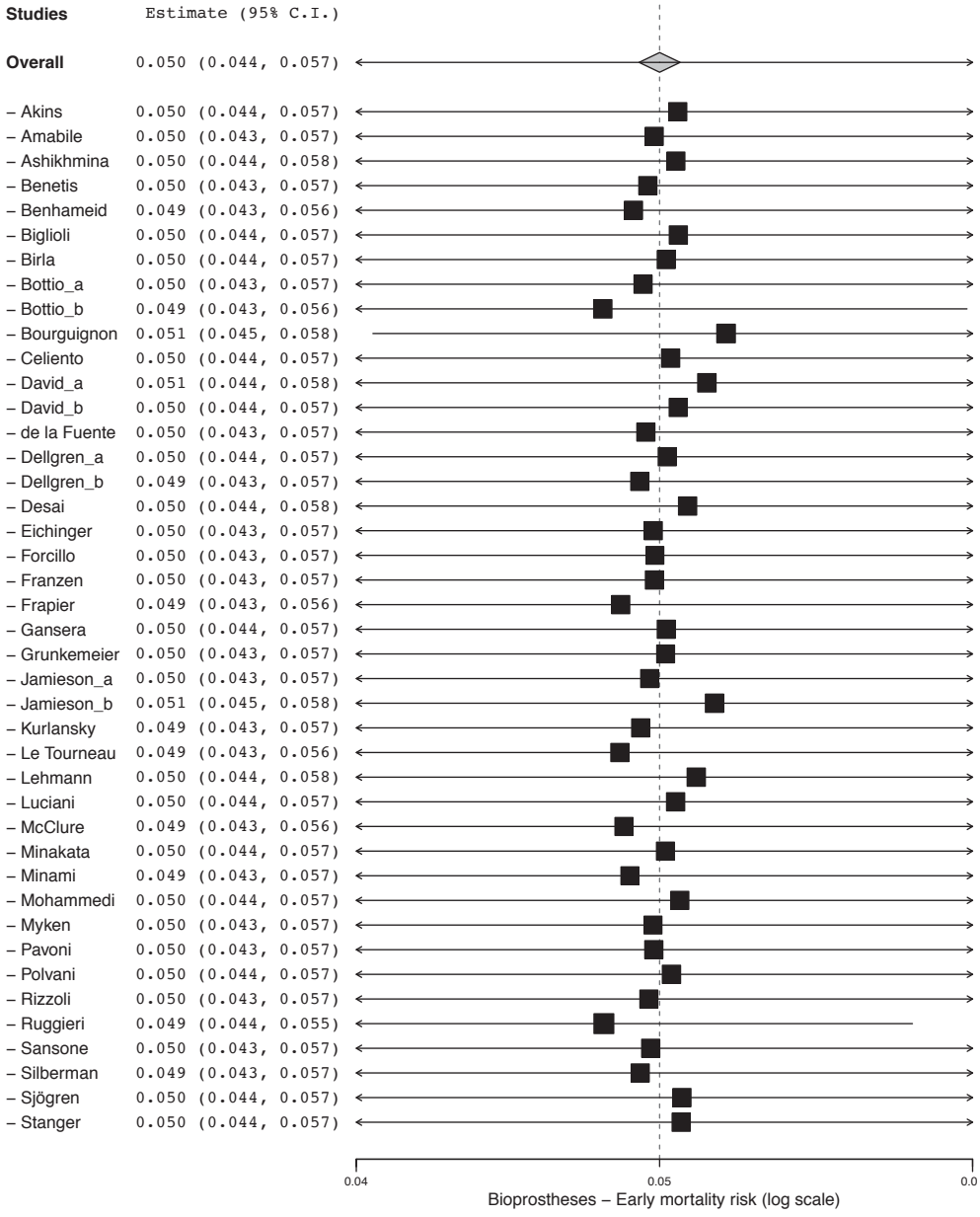
95% confidence intervals provided in parentheses. SVD: structural valve deterioration. NSVD: non-structural valve dysfunction. SUUD: sudden unexpected unexplained death. CABG: coronary atery bypass grafting. *≤1 study reported this outcome measure.

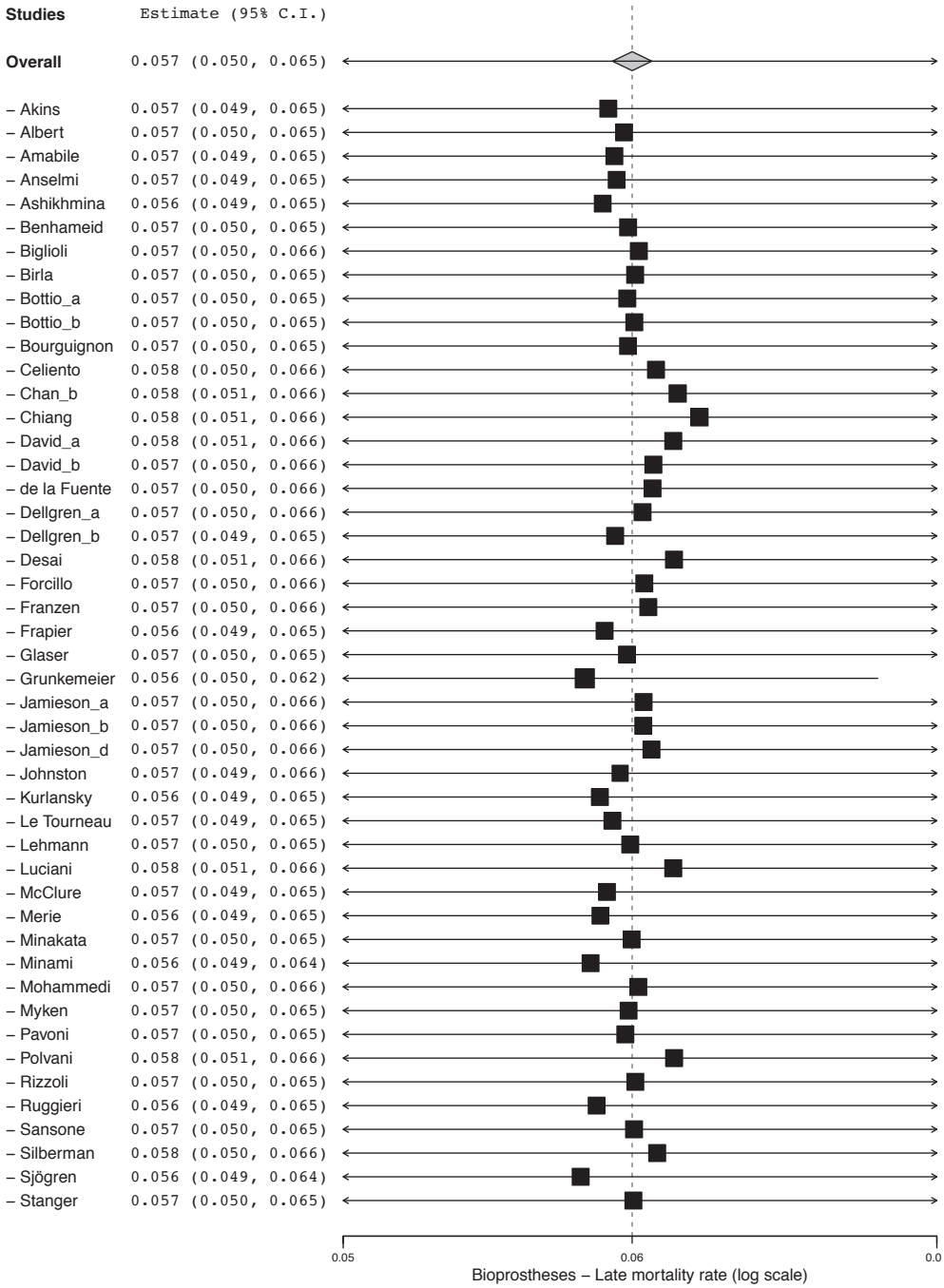
Table S18. Subgroup analysis prospective versus retrospective studies on allografts.

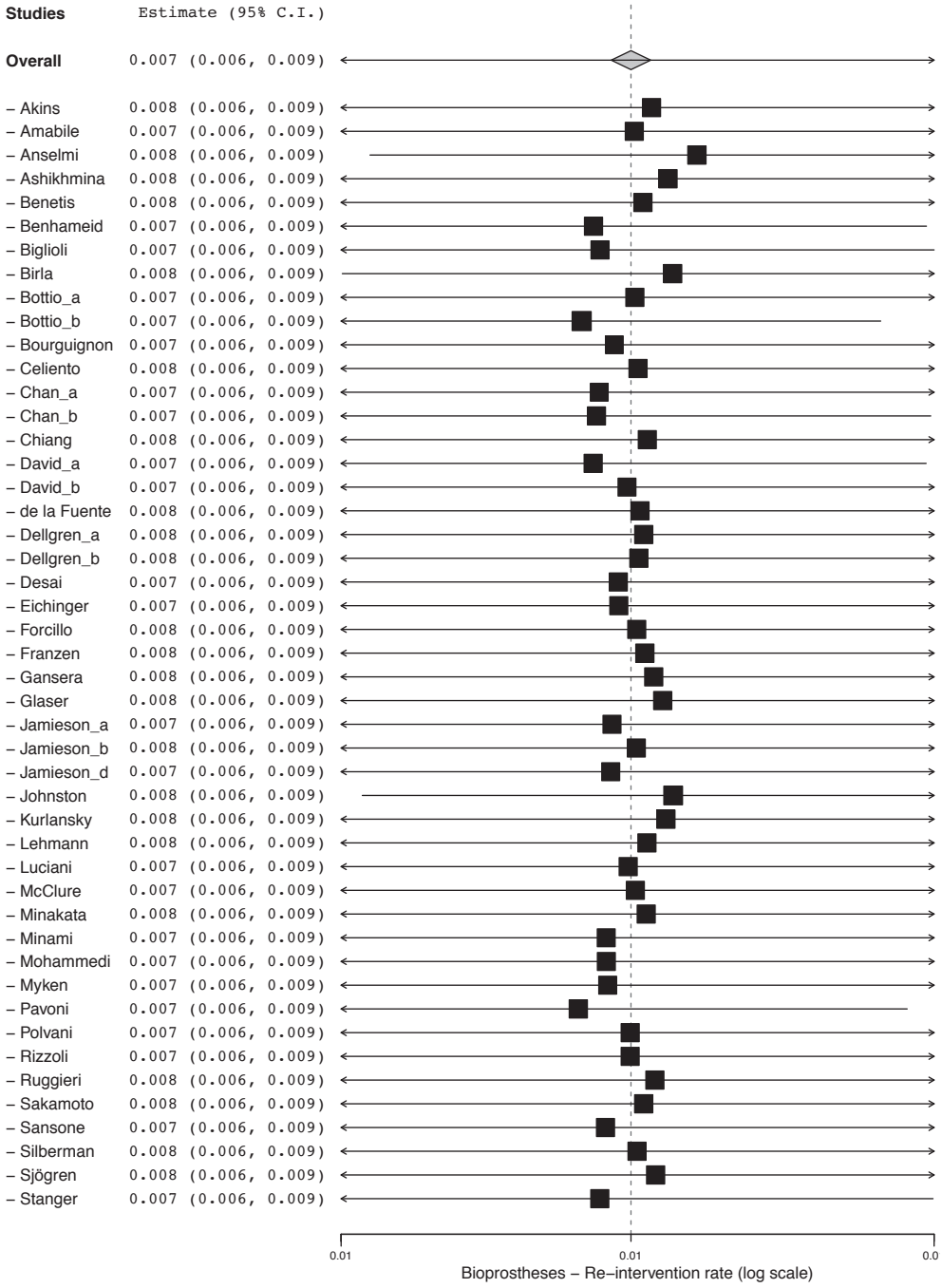
ALLOGRAFTS	Prospective studies	Reported in n studies	Retrospective studies	Reported in n studies
Study characteristics				
No. of studies	3		11	
No. of patients	861		3,011	
Mean follow-up, y ±SD	11.6 ± 1.5	3	7.6 ± 3.5	11
Mean age, y ±SD	44.5 ± 13.1	3	50.1 ± 12.9	10
Male, %	71.3	3	68.8	10
Concomitant CABG, %	10.8	2	12.6	7
Early mortality, %				
Early mortality	5.91 (4.52-7.73)	3	4.51 (2.85-7.15)	11
Early valve-related events, %				
SVD	*	0	*	0
NSVD	*	0	*	0
Valve thrombosis	*	0	*	0
Thromboembolism	*	0	*	0
Reexploration for bleeding	*	1	*	0
Endocarditis	*	0	*	1
Late mortality, %/year				
Late mortality	1.00 (0.42-2.38)	3	2.46 (2.21-2.74)	7
Cardiac late mortality	*	1	1.03 (0.87-1.22)	7
Valve-related late mortality	0.34 (0.15-0.78)	3	0.47 (0.32-0.67)	6
SUUD	*	1	*	1
Late valve-related events, %/year				
SVD	*	0	2.26 (1.02-4.97)	3
NSVD	*	0	*	1
Valve thrombosis	*	0	*	0
Thromboembolism	0.23 (0.14-0.40)	2	0.80 (0.35-1.84)	3
Bleeding	*	1	0.17 (0.08-0.35)	2
Endocarditis	*	1	0.40 (0.28-0.56)	4
Re-interventions, %/year				
Total	1.45 (0.71-2.95)	3	1.99 (1.62-2.44)	10
Valve-related	1.39 (0.67-2.90)	3	1.96 (1.59-2.42)	10
SVD	0.98 (0.22-4.46)	2	1.22 (0.85-1.76)	6
NSVD	0.40 (0.29-0.55)	2	0.03 (0.01-0.09)	5
Valve thrombosis	0.02 (0.00-0.10)	3	0.03 (0.01-0.09)	5
Endocarditis	0.20 (0.07-0.55)	3	0.29 (0.20-0.42)	6

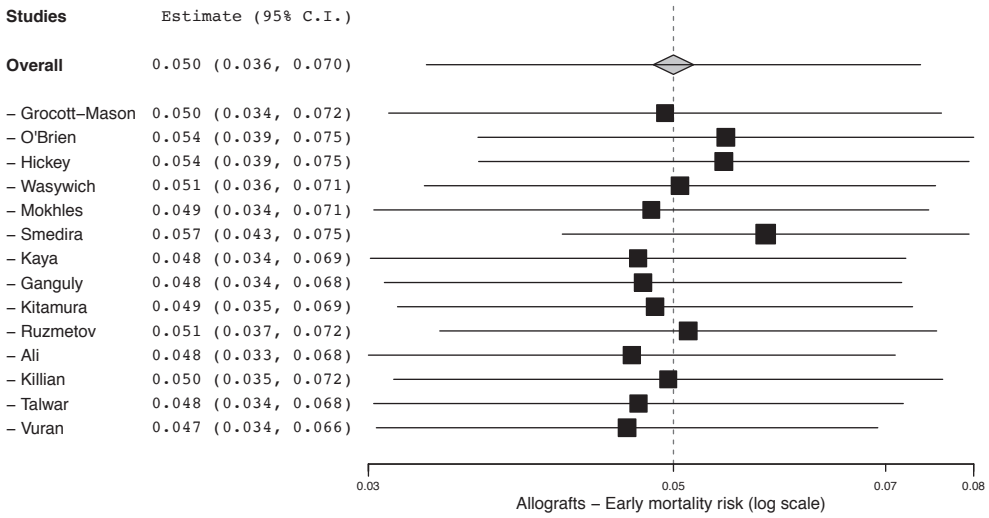
95% CIs of the pooled estimates are provided in parentheses. SVD: structural valve deterioration. NSVD: non-structural valve dysfunction. SUUD: sudden unexpected unexplained death. CABG: coronary atery bypass grafting. *≤1 study reported this outcome measure.

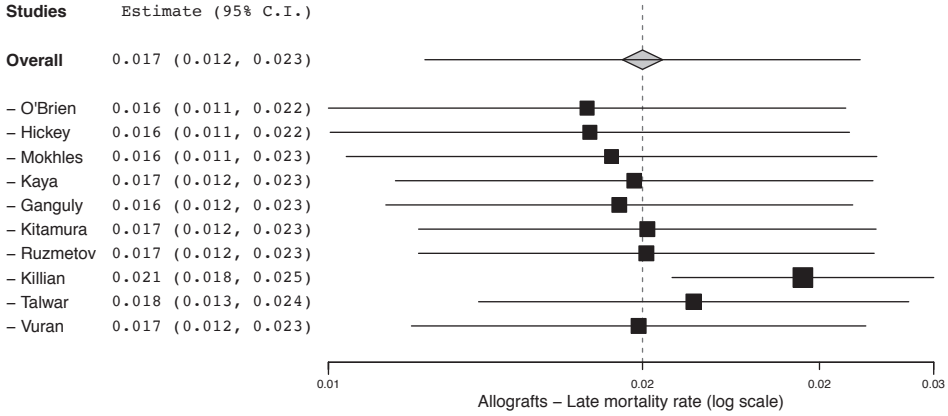
Forest plots of leave-one-out analysis

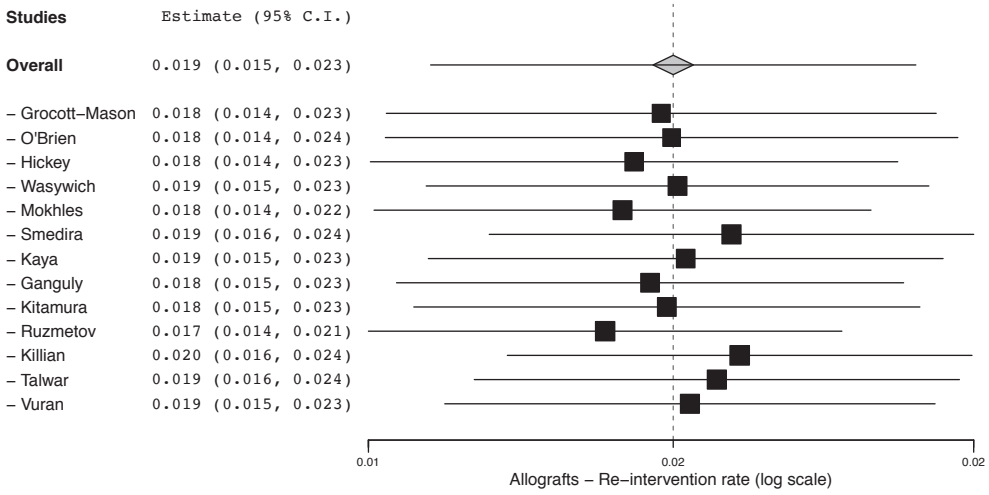



Studies
Estimate (95% C.I.)
Overall 0.057 (0.050, 0.065)
– Akins 0.057 (0.049, 0.065)
– Albert 0.057 (0.050, 0.065)
– Amabile 0.057 (0.049, 0.065)
– Anselmi 0.057 (0.049, 0.065)
– Ashikhmina 0.056 (0.049, 0.065)
– Benhameid 0.057 (0.050, 0.065)
– Biglioli 0.057 (0.050, 0.066)
– Birla 0.057 (0.050, 0.065)
– Bottio_a 0.057 (0.050, 0.065)
– Bottio_b 0.057 (0.050, 0.065)
– Bourguignon 0.057 (0.050, 0.065)
– Celiento 0.058 (0.050, 0.066)
– Chan_b 0.058 (0.051, 0.066)
– Chiang 0.058 (0.051, 0.066)
– David_a 0.058 (0.051, 0.066)
– David_b 0.057 (0.050, 0.066)
– de la Fuente 0.057 (0.050, 0.066)
– Dellgren_a 0.057 (0.050, 0.066)
– Dellgren_b 0.057 (0.049, 0.065)
– Desai 0.058 (0.051, 0.066)
– Forcillo 0.057 (0.050, 0.066)
– Franzen 0.057 (0.050, 0.066)
– Frapier 0.056 (0.049, 0.065)
– Glaser 0.057 (0.050, 0.065)
– Grunkemeier 0.056 (0.050, 0.062)
– Jamieson_a 0.057 (0.050, 0.066)
– Jamieson_b 0.057 (0.050, 0.066)
– Jamieson_d 0.057 (0.050, 0.066)
– Johnston 0.057 (0.049, 0.066)
– Kurlansky 0.056 (0.049, 0.065)
– Le Tourneau 0.057 (0.049, 0.065)
– Lehmann 0.057 (0.050, 0.065)
– Luciani 0.058 (0.051, 0.066)
– McClure 0.057 (0.049, 0.065)
– Merie 0.056 (0.049, 0.065)
– Minakata 0.057 (0.050, 0.065)
– Minami 0.056 (0.049, 0.064)
– Mohammedi 0.057 (0.050, 0.066)
– Myken 0.057 (0.050, 0.065)
– Pavoni 0.057 (0.050, 0.065)
– Polvani 0.058 (0.051, 0.066)
– Rizzoli 0.057 (0.050, 0.065)
– Ruggieri 0.056 (0.049, 0.065)
– Sansone 0.057 (0.050, 0.065)
– Silberman 0.058 (0.050, 0.066)
– Sjögren 0.056 (0.049, 0.064)
– Stanger 0.057 (0.050, 0.065)
0.05
0.06
0.0
Bioprostheses – Late mortality rate (log scale)

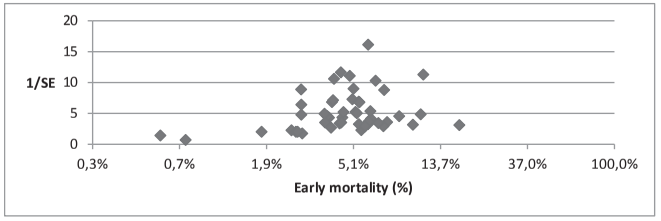

Studies
Estimate (95% C.I.)
Overall 0.007 (0.006, 0.009)
– Akins 0.008 (0.006, 0.009)
– Amabile 0.007 (0.006, 0.009)
– Anselmi 0.008 (0.006, 0.009)
– Ashikhmina 0.008 (0.006, 0.009)
– Benetis 0.008 (0.006, 0.009)
– Benhameid 0.007 (0.006, 0.009)
– Biglioli 0.007 (0.006, 0.009)
– Birla 0.008 (0.006, 0.009)
– Bottio_a 0.007 (0.006, 0.009)
– Bottio_b 0.007 (0.006, 0.009)
– Bourguignon 0.007 (0.006, 0.009)
– Celiento 0.008 (0.006, 0.009)
– Chan_a 0.007 (0.006, 0.009)
– Chan_b 0.007 (0.006, 0.009)
– Chiang 0.008 (0.006, 0.009)
– David_a 0.007 (0.006, 0.009)
– David_b 0.007 (0.006, 0.009)
– de la Fuente 0.008 (0.006, 0.009)
– Dellgren_a 0.008 (0.006, 0.009)
– Dellgren_b 0.008 (0.006, 0.009)
– Desai 0.007 (0.006, 0.009)
– Eichinger 0.007 (0.006, 0.009)
– Forcillo 0.008 (0.006, 0.009)
– Franzen 0.008 (0.006, 0.009)
– Gansera 0.008 (0.006, 0.009)
– Glaser 0.008 (0.006, 0.009)
– Jamieson_a 0.007 (0.006, 0.009)
– Jamieson_b 0.008 (0.006, 0.009)
– Jamieson_d 0.007 (0.006, 0.009)
– Johnston 0.008 (0.006, 0.009)
– Kurlansky 0.008 (0.006, 0.009)
– Lehmann 0.008 (0.006, 0.009)
– Luciani 0.007 (0.006, 0.009)
– McClure 0.007 (0.006, 0.009)
– Minakata 0.008 (0.006, 0.009)
– Minami 0.007 (0.006, 0.009)
– Mohammedi 0.007 (0.006, 0.009)
– Myken 0.007 (0.006, 0.009)
– Pavoni 0.007 (0.006, 0.009)
– Polvani 0.007 (0.006, 0.009)
– Rizzoli 0.007 (0.006, 0.009)
– Ruggieri 0.008 (0.006, 0.009)
– Sakamoto 0.008 (0.006, 0.009)
– Sansone 0.007 (0.006, 0.009)
– Silberman 0.008 (0.006, 0.009)
– Sjögren 0.008 (0.006, 0.009)
– Stanger 0.007 (0.006, 0.009)
0.01
0.01
0.0
Bioprostheses – Re–intervention rate (log scale)

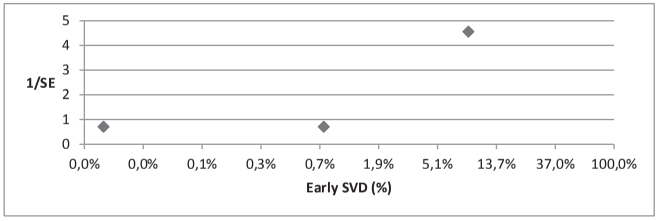

Studies
Estimate (95% C.I.)
Overall 0.050 (0.036, 0.070)
– Grocott–Mason 0.050 (0.034, 0.072)
– O'Brien 0.054 (0.039, 0.075)
– Hickey 0.054 (0.039, 0.075)
– Wasywich 0.051 (0.036, 0.071)
– Mokhles 0.049 (0.034, 0.071)
– Smedira 0.057 (0.043, 0.075)
– Kaya 0.048 (0.034, 0.069)
– Ganguly 0.048 (0.034, 0.068)
– Kitamura 0.049 (0.035, 0.069)
– Ruzmetov 0.051 (0.037, 0.072)
– Ali 0.048 (0.033, 0.068)
– Killian 0.050 (0.035, 0.072)
– Talwar 0.048 (0.034, 0.068)
– Vuran 0.047 (0.034, 0.066)
0.03
0.05
0.07
0.08
Allografts – Early mortality risk (log scale)

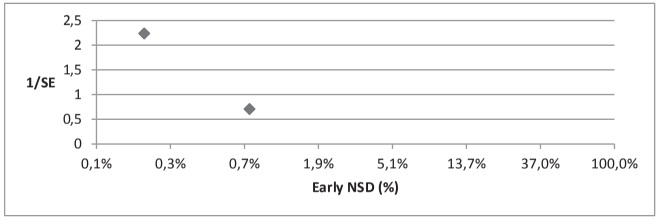

Studies
Estimate (95% C.I.)
Overall 0.017 (0.012, 0.023)
– O'Brien 0.016 (0.011, 0.022)
– Hickey 0.016 (0.011, 0.022)
– Mokhles 0.016 (0.011, 0.023)
– Kaya 0.017 (0.012, 0.023)
– Ganguly 0.016 (0.012, 0.023)
– Kitamura 0.017 (0.012, 0.023)
– Ruzmetov 0.017 (0.012, 0.023)
– Killian 0.021 (0.018, 0.025)
– Talwar 0.018 (0.013, 0.024)
– Vuran 0.017 (0.012, 0.023)
0.01
0.02
0.02
0.03
Allografts – Late mortality rate (log scale)

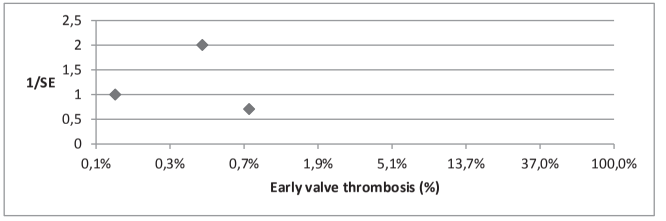

Studies
Estimate (95% C.I.)
Overall 0.019 (0.015, 0.023)
– Grocott–Mason 0.018 (0.014, 0.023)
– O'Brien 0.018 (0.014, 0.024)
– Hickey 0.018 (0.014, 0.023)
– Wasywich 0.019 (0.015, 0.023)
– Mokhles 0.018 (0.014, 0.022)
– Smedira 0.019 (0.016, 0.024)
– Kaya 0.019 (0.015, 0.023)
– Ganguly 0.018 (0.015, 0.023)
– Kitamura 0.018 (0.015, 0.023)
– Ruzmetov 0.017 (0.014, 0.021)
– Killian 0.020 (0.016, 0.024)
– Talwar 0.019 (0.016, 0.024)
– Vuran 0.019 (0.015, 0.023)
0.01
0.02
0.02
Allografts – Re–intervention rate (log scale)

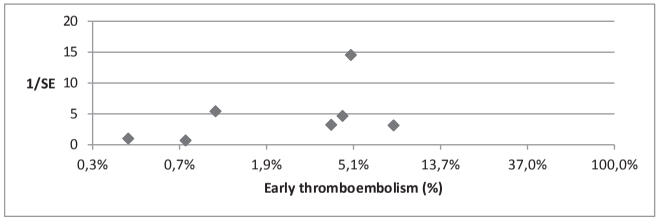
Funnel plots
Bioprostheses

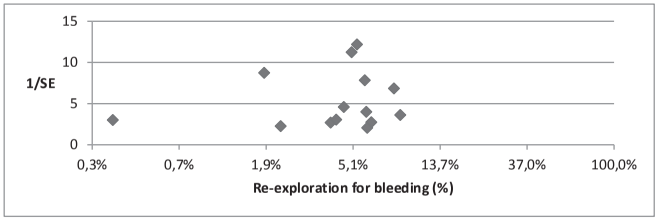


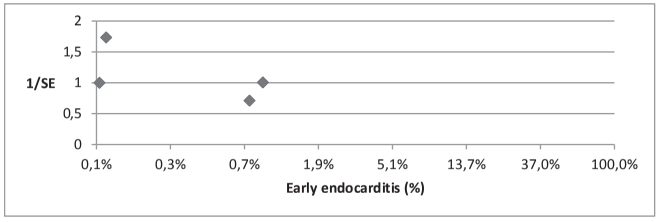


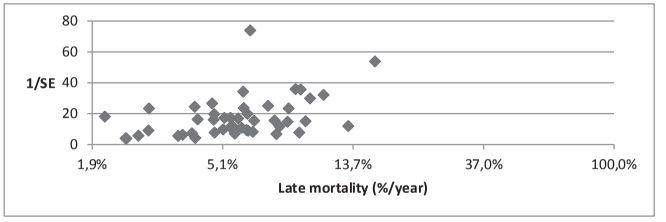


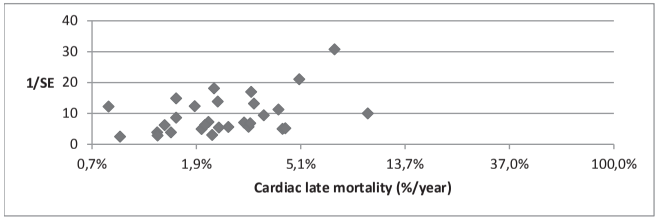


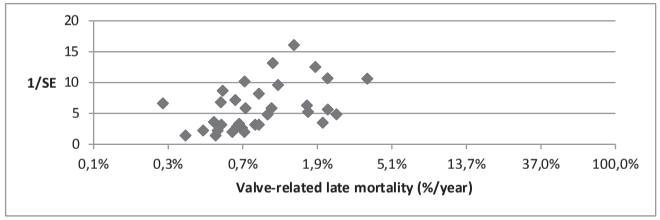


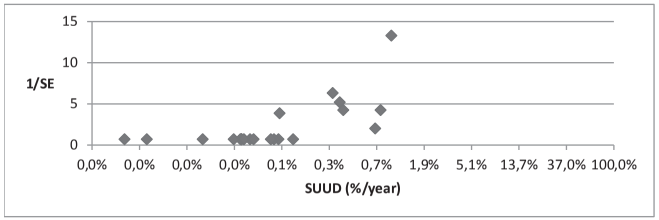


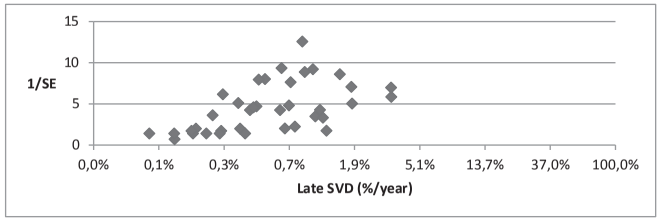


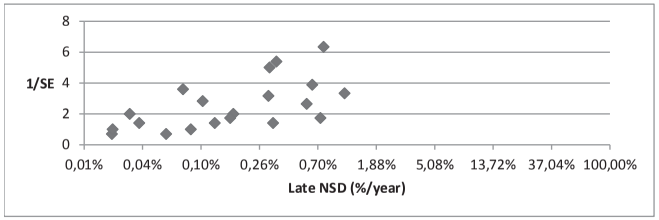


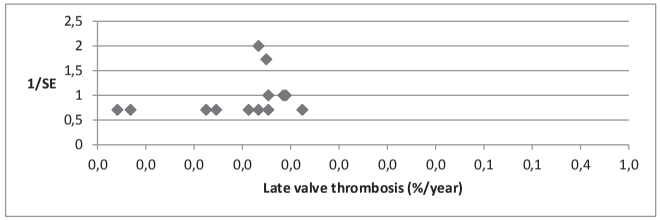

1/SE
0
10
20
30
40
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Cardiac late mortality (%/year)

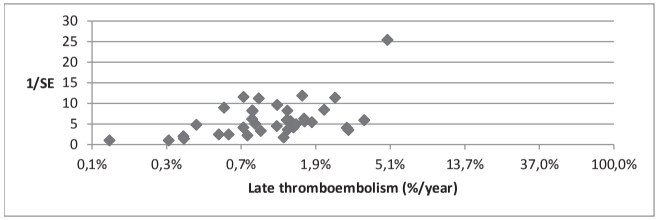

1/SE
0
5
10
15
20
0,1%
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Valve-related late mortality (%/year)

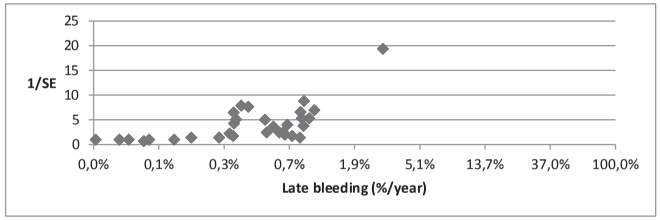

1/SE
0
5
10
15
0,0%
0,0%
0,0%
0,0%
0,1%
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
SUUD (%/year)

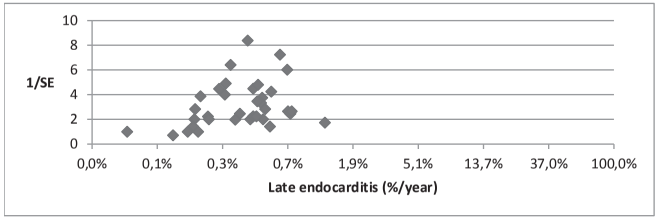

1/SE
0
5
10
15
0,0%
0,1%
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Late SVD (%/year)

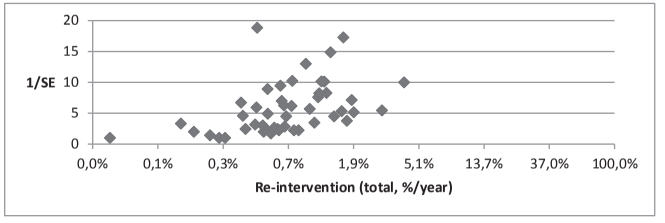

1/SE
0
2
4
6
8
0,01%
0,04%
0,10%
0,26%
0,70%
1,88%
5,08%
13,72%
37,04%
100,00%
Late NSD (%/year)

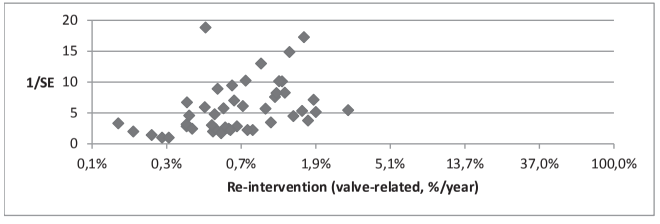

1/SE
0
0,5
1
1,5
2
2,5
0,0
0,0
0,0
0,0
0,0
0,0
0,0
0,0
0,1
0,1
0,4
1,0
Late valve thrombosis (%/year)

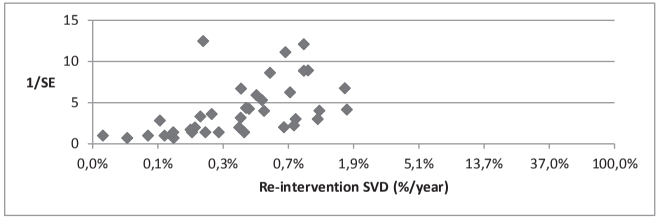

1/SE
0
5
10
15
20
25
30
0,1%
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Late thromboembolism (%/year)

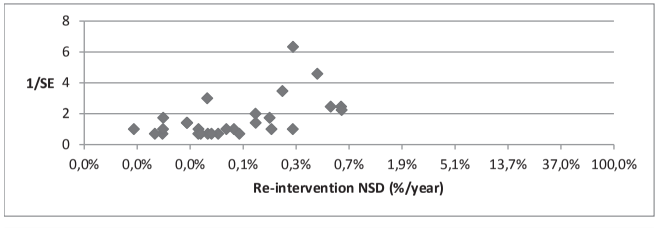

1/SE
0
5
10
15
20
25
0,0%
0,1%
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Late bleeding (%/year)

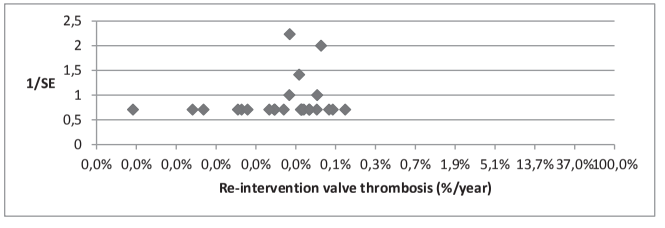

1/SE
0,0% 0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Late endocarditis (%/year)

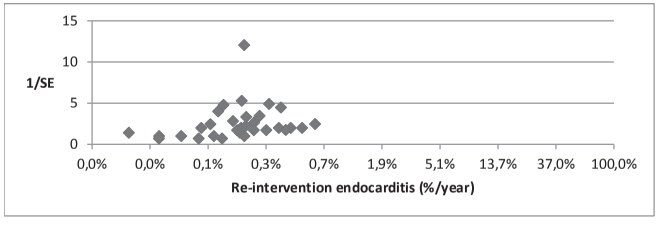

1/SE
0,0% 0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention (total, %/year)


1/SE
0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention (valve-related, %/year)

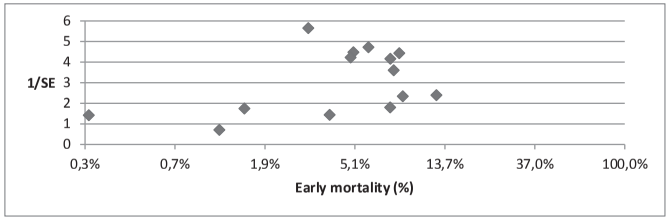

1/SE
0,0% 0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention SVD (%/year)

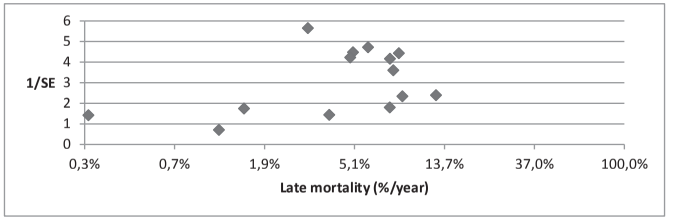

1/SE
0,0% 0,0% 0,0% 0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention NSD (%/year)

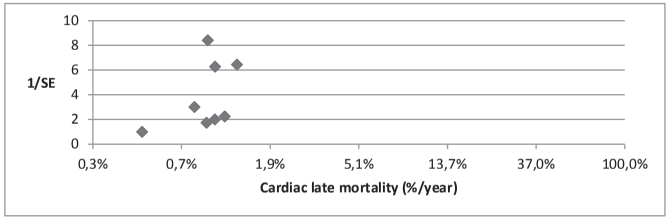

1/SE
0,0% 0,0% 0,0% 0,0% 0,0% 0,0% 0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention valve thrombosis (%/year)

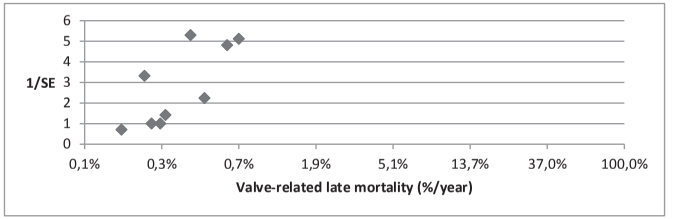

1/SE
0,0% 0,0% 0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention endocarditis (%/year)

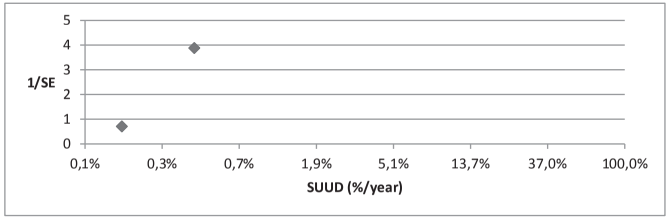
Allografts

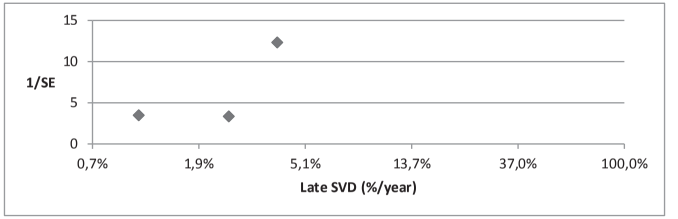

1/SE
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Early mortality (%)

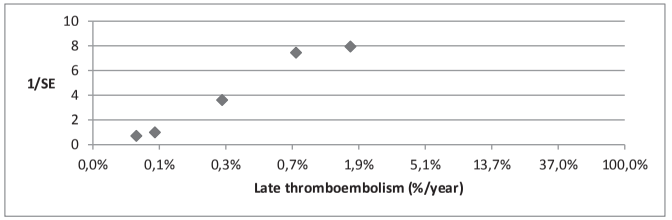

1/SE
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Late mortality (%/year)

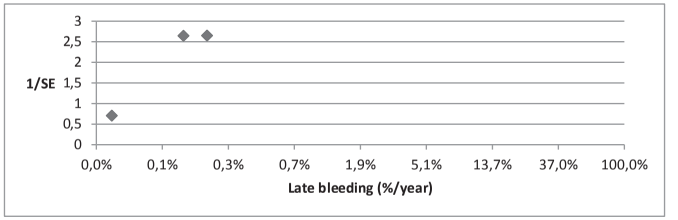

1/SE
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Cardiac late mortality (%/year)

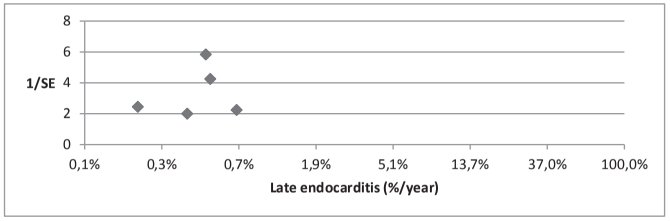

1/SE
0,1%
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Valve-related late mortality (%/year)

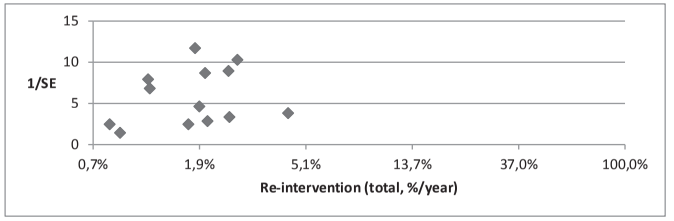

1/SE
0,1%
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
SUUD (%/year)

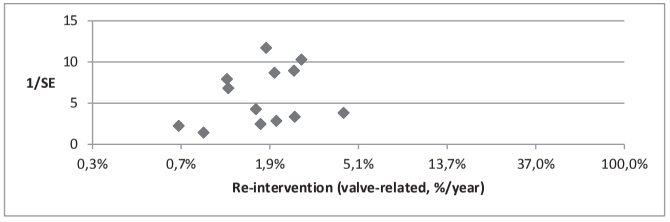

1/SE
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Late SVD (%/year)

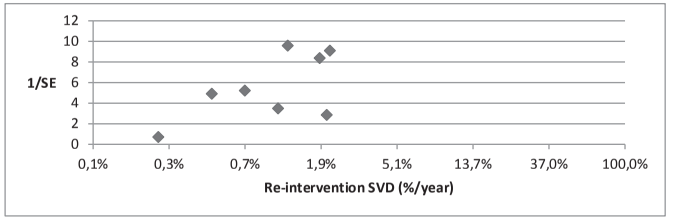

1/SE
0,0%
0,1%
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Late thromboembolism (%/year)

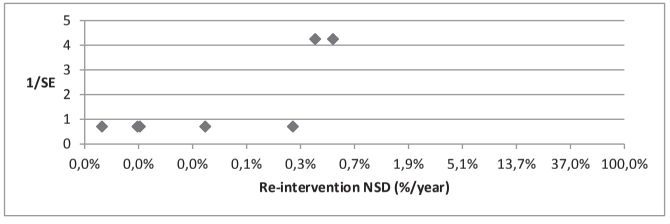

1/SE
0,0%
0,1%
0,3%
0,7%
1,9%
5,1%
13,7%
37,0%
100,0%
Late bleeding (%/year)

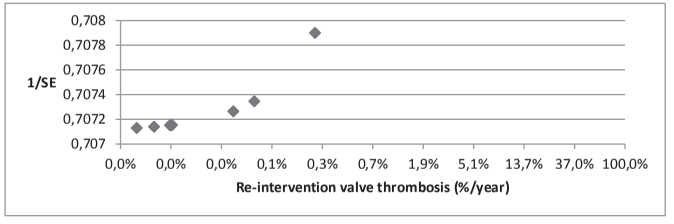

1/SE
8
6
4
2
0
0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Late endocarditis (%/year)

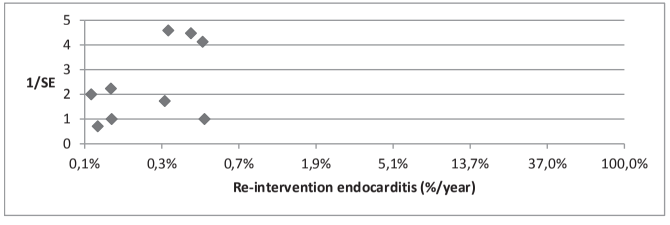

1/SE
15
10
5
0
0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention (total, %/year)

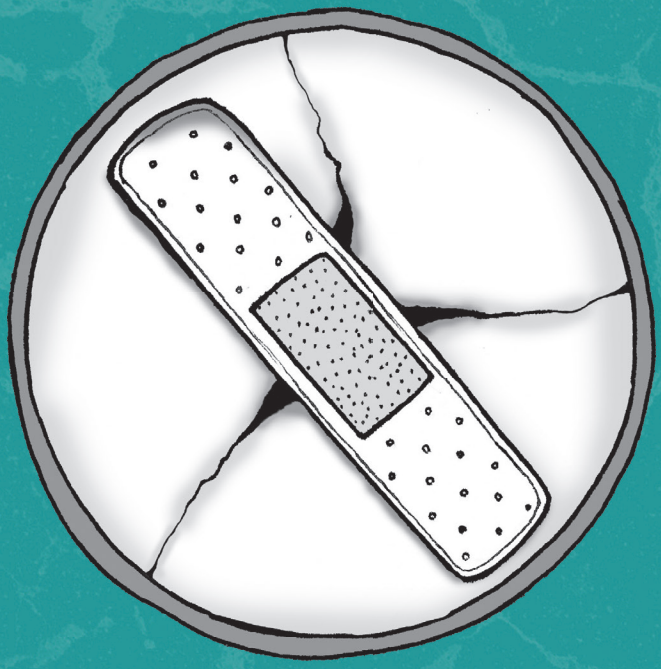

1/SE
15
10
5
0
0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention (valve-related, %/year)


1/SE
12
10
8
6
4
2
0
0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention SVD (%/year)


1/SE
5
4
3
2
1
0
0,0% 0,0% 0,0% 0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention NSD (%/year)


1/SE
0,708
0,7078
0,7076
0,7074
0,7072
0,707
0,0% 0,0% 0,0% 0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention valve thrombosis (%/year)


1/SE
5
4
3
2
1
0
0,1% 0,3% 0,7% 1,9% 5,1% 13,7% 37,0% 100,0%
Re-intervention endocarditis (%/year)



5

Bioprosthetic aortic valve replacement in the elderly

Meta-analysis & microsimulation

Simone A. Huygens, Jonathan R.G. Etnel, Milad Hanif, Jos A. Bekkers, Ad J.J.C. Bogers, Maureen P.M.H. Rutten-van Mölken, Johanna J.M. Takkenberg.

JTCVS. In press.

ABSTRACT

Objective: To support decision-making in aortic valve replacement (AVR) in elderly patients, we provide a comprehensive overview of outcome after AVR with bioprostheses.

Methods: A systematic review was conducted of studies reporting clinical outcome after AVR with bioprostheses in elderly patients (mean age ≥70 years; minimum age ≥65 years) published between January, 1, 2000 to January 9, 2016. Reported event rates and time-to-event data were pooled and entered into a microsimulation model to calculate life expectancy and lifetime event risks.

Results: Forty-two studies reporting on 34 patient cohorts were included, encompassing a total of 12,842 patients with 55,437 patient-years of follow-up (pooled mean follow-up 5.0±3.3 years). Pooled mean age was 76.5±5.5 years. Pooled early mortality risk was 5.42% (95% confidence interval [CI]:4.49-6.55), thromboembolism rate was 1.83%/year (95%CI: 1.28-3.61), and bleeding rate was 0.75%/year (95%CI: 0.50-1.11). Structural valve deterioration (SVD) was based on pooled time to SVD data (Gompertz; shape: 0.124, rate: 0.003). For a 75-year old patient, this translated to an estimated life expectancy of 9.8 years (general population: 10.2 years) and lifetime risks of bleeding of 7%, thromboembolism of 17%, and re-intervention of 9%.

Conclusions: The low risks of SVD and re-intervention support the use of bioprostheses in elderly patients in need of AVR. The estimated life expectancy after AVR was comparable with the general population. The results of this study informs patients and clinicians about the expected outcomes after bioprosthetic AVR and thereby supports treatment decision-making. Furthermore, our results can be used as a benchmark for long-term outcomes after transcatheter aortic valve implantation in patients who were eligible for surgery and other (future) alternative treatments (e.g. tissue-engineered heart valves).

INTRODUCTION

Native aortic valve degeneration represents a major public health burden in the aging population of developed countries. In patients above 75 years, the prevalence of aortic stenosis is 2.8% and of aortic regurgitation 2.0%.[1] Due to the ageing population and improvements in healthcare, it is expected that the number of aortic valve implantations will increase, especially in elderly patients.[1, 2]

When the degenerated aortic valve needs replacement, there are two widely used treatment options for elderly patients: surgical aortic valve replacement (AVR) or transcatheter aortic valve implantation (TAVI). For surgical AVR, two types of valve substitutes are available: bioprostheses and mechanical prostheses. Current clinical guidelines recommend bioprostheses in patients above 65[3]/70[4] years because their life expectancy is usually shorter than the durability of the valve and therefore they will probably not experience the disadvantages of bioprostheses (i.e. increased risk of structural valve deterioration (SVD) and subsequent risk of re-intervention).[3, 4] Bioprostheses are preferred over mechanical prostheses because they are not accompanied with an increased risk of thromboembolism (TE) and subsequent need of lifelong anticoagulation which carries an increased risk of bleeding events.[3, 4]

Ideally, the choice of heart valve substitute should be a shared decision, where the patient is fully informed about the risks and benefits associated with each type of valve substitute and is able to weigh these in relation to his/her values and goals in life.[3, 4] However, a comprehensive overview of published evidence on long-term outcome after AVR in elderly patients to guide this decision-making is lacking. We therefore provide a systematic review and meta-analysis of reported outcomes after AVR with bioprostheses in elderly patients applying the latest methods of meta-analysis and calculating microsimulation-based estimates of age-specific life expectancy and lifetime risks of valve-related events.

METHODS

Search strategy and study selection

This systematic review was conducted according to PRISMA guidelines[5] and registered in PROSPERO (CRD42017054849). On September 1, 2016, Embase, MEDLINE, The Cochrane Central, Google Scholar, Web-Of-Science and Pubmed publisher databases were searched by a biomedical information specialist using keywords regarding outcomes of AVR with bioprostheses (Supplementary Material). Titles and abstracts were independently screened by two reviewers (SH, MH). Inclusion criteria were

observational studies or randomized controlled trials reporting on outcomes of isolated AVR (maximum 10% multiple valve replacement was allowed) with bioprostheses of at least 20 patients with mean age≥70 and minimum age ≥65 published in or after the year 2000. Studies were excluded if they exclusively enrolled patients with pre-existing comorbidities or certain prosthesis sizes or only reported results of propensity matched study populations (because of less generalizability of the study population). In case of multiple publications on the same patient population, the publication with most follow-up patient-years and/or overall completeness of data was included. In case of disagreement between the reviewers, an agreement was negotiated.

Data extraction

Data extraction was performed with independently by two researchers (SH, MH) using Microsoft Office Excel 2011 (Microsoft Corp, Redmond, Wash) and then jointly verified. Recorded study characteristics, baseline patient and procedural characteristics, and outcome measures are listed in Supplementary Material. Occurrence of valve-related events, re-intervention, and mortality were documented according to the 2008 American Association for Thoracic Surgery/European Association for Cardio-Thoracic Surgery/Society of Thoracic Surgeons guidelines.[6] Early outcome events were defined as occurring within the first 30 postoperative days, regardless of the patient's location. Late outcome events were defined as occurring after the first 30 postoperative days. If total follow-up duration in patient-years was not reported, it was calculated by multiplying the mean follow-up with the number of patients of that study.

Statistical analyses

Statistical software used is listed in Supplementary Material. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as counts and percentages. Linearized event occurrence rates are presented as percentages per year.

Meta-analysis

Pooled baseline patient characteristics were calculated with the use of sample size weighting. Early risks of mortality and valve-related events and linearized occurrence rates of late mortality, valve-related events, and re-intervention were calculated for each individual study and pooled using the inverse variance method in a random-effects model. In the random-effects model, the Der Simonian and Laird method was used for estimating the between studies variance.[7] Outcomes were pooled on a logarithmic scale, as the Shapiro–Wilk test revealed a significantly skewed distribution among the included studies in the majority of outcome measures. Inverse variance weighting was conducted according to the number of patients for early mortality and according to the number of follow-up patient-years for late events. In case an event was reported

not to occur in an individual study, it was assumed that 0.5 patient experienced that event for the purpose of inverse variance weighting.

Pooled Kaplan-Meier time-to-event meta-analysis was conducted by extracting and combining estimates of individual patient time-to-event data from published Kaplan-Meier curves. Published Kaplan-Meier curves were digitized. An estimate of the individual patient time-to-event data was then extracted from the digitized curve coordinates, assuming a constant rate of censorship between each time point at which the number of patients at risk were specified.[8] If there were no Kaplan-Meier curves available, but time points of each event were reported or there were no events, the individual patient time-to-event data was manually reconstructed up to a maximum follow-up of the mean follow-up plus two standard deviations, under the same assumption of a constant rate of censorship. Reconstructed individual patient time-to-event data of each study were then combined.

Heterogeneity

The Cochrane-Q statistic and I^2 statistic were used to assess heterogeneity between studies. Potential causes of heterogeneity were explored with univariable random effects meta-regression in the main outcome measures with significant heterogeneity and more than three studies reporting the outcome measure. The following covariates were explored: study design (retrospective/prospective), region of origin, median year of valve implantation period, mean follow-up duration, mean patient age, proportion of male patients, emergency surgery, preoperative New York Heart Association class, hemodynamics, and concomitant coronary artery bypass grafting. The influence of potential publication bias on pooled outcomes was investigated by conducting sensitivity analyses where the quartile of studies with the smallest sample size was temporarily excluded.

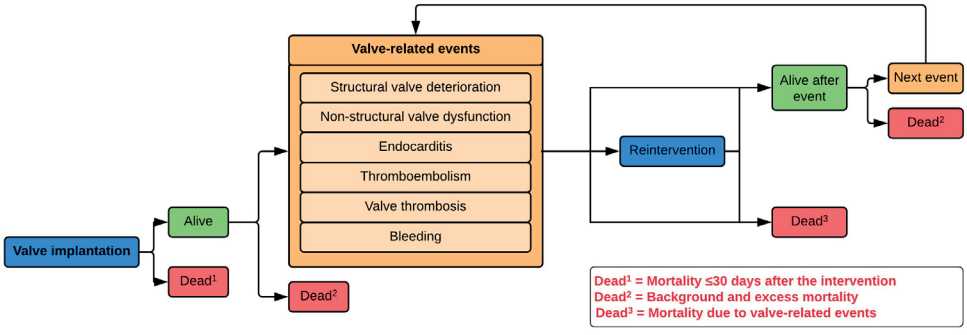


Figure 1. Schematic overview of microsimulation model.

Microsimulation

A microsimulation model parametrized with the pooled outcomes of our meta-analysis was used to extrapolate the results from the meta-analysis to age-specific life expectancy and lifetime risk of valve-related morbidity (Figure 1).[9] The risks of mortality and re-intervention as a direct result of the events were derived from a study on patients after bioprosthetic AVR (mean age: 70 years).[10]

The occurrence rates of valve-related events had to be extrapolated beyond the observation period of the meta-analysis. The occurrence rate of SVD after bioprosthetic AVR was modeled by fitting a Gompertz distribution to our pooled time-to-event data (Figure S1), showing an increasing occurrence rate of SVD over time. There was no time-to-event data available for other valve-related events (non-structural valve dysfunction, endocarditis, thromboembolism, valve thrombosis, and endocarditis); therefore, we assumed constant hazard rates for these events.

Total mortality consists of death due to valve-related events and death due to non-valve related causes. Death due to non-valve related causes consists of background mortality in the general population and excess mortality not directly resulting from valve-related events. The background mortality of the general population was obtained for the pooled median year of intervention among included studies (1998, assuming a constant incidence rate over time in each study), adjusted for sex (54.8% male), and the regions of origin of the included study populations (Europe: 52%, North America: 45%; Asia: 3%).[11, 12]

To estimate the hazard ratios of additional excess mortality not directly resulting from valve-related events relative to background mortality, we compared the survival simulated by the microsimulation model with the observed survival in our meta-analysis of time-to-event data (temporarily excluding early mortality, as early mortality was a separate input in our microsimulation model). In these microsimulations, we repeatedly simulated the survival of 10,000 patients with a mean age and proportion of males of the study population using the same background mortality and mortality due to valve-related events, but with various hazard ratios of excess mortality. The hazard ratio that resulted in the smallest difference between the simulated and observed survival according to the least squares method was chosen as the appropriate hazard ratio for excess mortality. This hazard ratio was assumed to be constant over time.

To obtain age-specific estimates of life expectancy and lifetime risk of valve-related events, the microsimulation model simulated cohorts of 10,000 patients aged 75 or 85 years, of which 54.8% were males (i.e. pooled male/female ratio included studies).

To reflect the uncertainty in the input parameters of the microsimulation model (second-order uncertainty) and to describe what this means for uncertainty in the outcomes, we performed probabilistic sensitivity analysis. In the probabilistic sensitivity analysis, the model was run for 500 different sets of randomly drawn input parameters with a sample size of 1000 patients per set. The values of the input parameters of the model were randomly drawn from the following distributions: beta distribution for early mortality risk and probabilities of re-intervention and death after events, log-normal distributions for late events, and uniform distributions for the hazard ratio of mortality after re-intervention and excess mortality (varied with +/- 10%). For each set of coefficients, the mean outcomes over the 1000 patients was recorded and the mean and the 2.5% and 97.5% percentile (credible interval) over all 500 mean values for each outcome were calculated.

To assess the internal validity of late survival outcomes of the model, the model was run for 10,000 patients with the pooled mean and standard deviation of age (76.5±5.5 years) and proportion of males (54.9%) of studies included in the pooled Kaplan-Meier survival curve. The Kaplan-Meier survival curve obtained from this model was then plotted against the pooled Kaplan-Meier survival curve of early survivors derived from our meta-analysis (temporarily excluding early mortality, as early mortality was a separate input in our microsimulation model).

RESULTS

Study selection

The systematic literature search identified 13,952 studies (Figure 2). After applying inclusion and exclusion criteria, the meta-analysis included 40 studies (34 patient cohorts) reporting on bioprostheses encompassing 12,842 patients (Table S1, references are provided in Supplementary Material). Multiple studies on 1 patient cohort were included when studies provided complementary information. Long-term follow-up was reported in 25 studies with a pooled mean follow-up of 5.0 years. Two studies [13, 14] were not included in the meta-analysis because of overlapping study populations, but these studies were included in the pooled Kaplan-Meier survival curve because the overlapping studies did not report Kaplan-Meier curves.

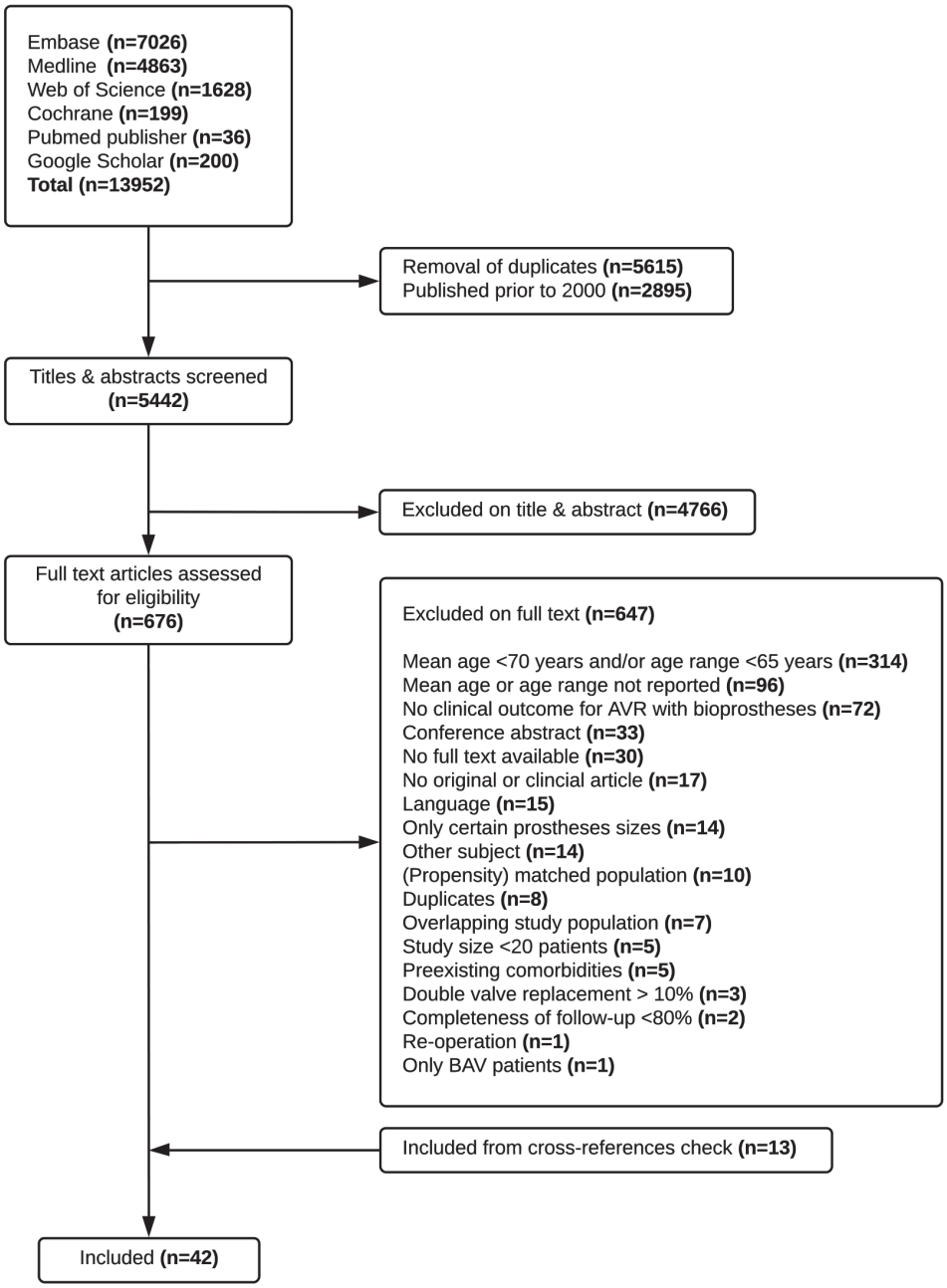


Figure 2. Flowchart of study selection. AVR: aortic valve replacement. BAV: bicuspid aortic valve.

Meta-analysis

Pooled estimates of patient and procedural characteristics, mortality, valve-related event and re-intervention risks and rates after AVR are presented in Table 1. The risks estimates of death and reoperation after valve-related events are presented in Table S2. Estimates of outcomes in individual studies are provided in Tables S3-5. Early events besides re-exploration for bleeding, stroke, myocardial infarction, and renal failure were reported too inconsistently to include in the analyses.

Figure 3 shows the pooled Kaplan-Meier survival curves after bioprosthetic AVR (n=6,096, mean follow-up 4.1±2.9 years). The 5-year survival was 72.1%. The survival curve of the general population was based on weighted survival tables of the general population adjusted to the regions of origin of the included study populations (Europe: 50%, United States: 45%, Asia: 5%) for the pooled median year of intervention among included studies (2001). The microsimulation model was run with these survival tables at the same mean age and proportion of males as the patient population and with valve-related mortality and events set to zero.[11, 15]

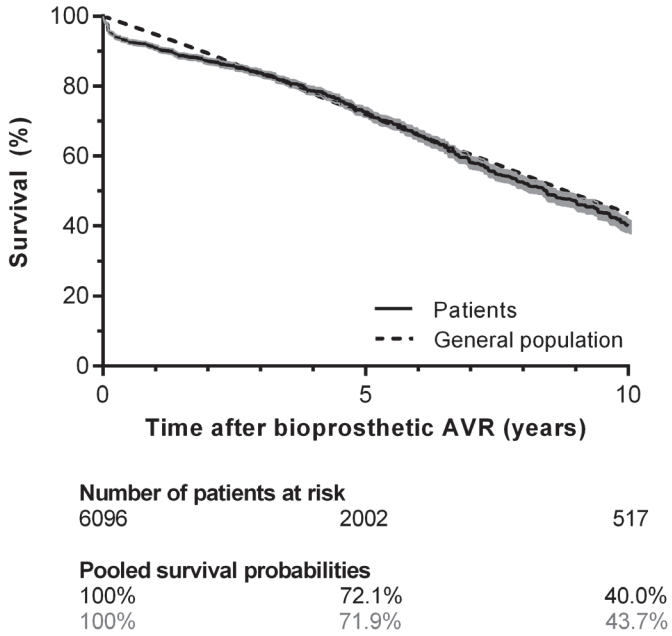


Figure 3. Pooled Kaplan-Meier survival curve of patients after bioprosthetic AVR (with 95% confidence interval) and the age- and sex-matched general population (dotted line).

AVR: aortic valve replacement

Table 1. Pooled estimates of patient and procedural characteristics and outcomes bioprosthetic AVR in elderly patients.

	Pooled estimate	Included studies (n)	I^2, % (χ^2 p-value)
Study characteristics			
Studies	40		
Patients	12,842	34	
Follow-up, years mean±SD	5.0±3.3	25	
Age, years mean±SD	76.5±5.5	30	
Male, n (%)	5,998 (54.9%)	31	
Emergency surgery, n (%)	172 (2.8%)	15	
NYHA class III/IV, n (%)	4,948 (71.5%)	22	
Hemodynamics, n (%)			
Stenosis	4,012 (65.7%)	17	
Regurgitation	1,059 (16.9%)	17	
Combined	1,002 (16.5%)	16	
Concomitant procedures, n (%)			
CABG	3,831(42.4%)	23	
Aortic surgery	187 (6.3%)	9	
Other valve repair/replacement	344 (5.0%)	11	
Other/unknown	183 (5.3%)	8	
Early mortality, %			
Early mortality	5.42 (4.49-6.55)	33	74 (0.000)
Early events, %			
Re-exploration for bleeding	4.18 (3.37-5.20)	13	32 (0.129)
Stroke	2.73 (1.75-4.28)	8	0 (0.700)
MI	0.88 (0.52-1.50)	6	0 (0.426)
Renal failure	6.60 (4.57-9.51)	10	69 (0.001)
Late events, %/year			
SVD	0.42 (0.17-1.05)	10	92 (0.000)
NSVD	0.47 (0.18-1.24)	8	78 (0.000)
Endocarditis	0.57 (0.43-0.76)	15	20 (0.235)
Thromboembolism	1.83 (1.28-2.61)	12	78 (0.000)
Valve thrombosis,	0.12 (0.04-0.39)	3	25 (0.262)
Bleeding	0.75 (0.50-1.11)	13	46 (0.035)
Re-intervention, %/year			
Re-intervention(valve-related)	0.56 (0.35-0.89)	13	87 (0.000)
Late mortality, %/year			
Total mortality	5.43 (4.47-6.60)	20	95 (0.000)
Cardiac mortality	1.76 (1.07-2.90)	10	93 (0.000)
Valve-related mortality	0.78 (0.41-1.46)	8	76 (0.000)
SUD,	0.41 (0.17-0.98)	7	54 (0.041)

95% confidence intervals of the pooled estimates are provided in parentheses. SD: standard deviation. CABG: coronary artery bypass grafting. NYHA: New York Heart Association. SVD: structural valve deterioration. NSVD: non-structural valve dysfunction. SUD: sudden unexplained death.

Microsimulation

Least squares regression of modeled versus observed survival revealed that the mortality not directly related to valve-related events (i.e. background and excess mortality) was 14% lower after bioprosthetic AVR (hazard ratio: 0.86) compared with the general population (Table S6). The age-specific estimates of (event-free) life-expectancy and lifetime risks of valve-related events based on microsimulation analyses are shown in Table 2, Figure 4, and Figure S2. The causes of re-intervention and death are presented in Table S7.

Figure S3 shows that the microsimulation model calibrated well with the pooled Kaplan-Meier curves of freedom from SVD and survival of early survivors from our meta-analysis. However, the microsimulation somewhat overestimated mortality within the first 5 years following bioprosthetic AVR and underestimated mortality in later years.

Table 2. Microsimulation results (event-free) life expectancy and lifetime risks on valve-related events after AVR with bioprostheses.

Age at surgery	75 years	85 years
Life expectancy, years*	9.8 (9.3-10.6)	5.6 (5.3-6.1)
Event-free life expectancy, years	8.2 (7.7-8.7)	5.0 (4.7-5.4)
Life time risks, %		
Structural valve deterioration	7.2 (5.0-10.3)	2.8 (1.6-4.2)
Non-structural valve dysfunction	4.4 (3.1-5.8)	2.6 (1.6-3.7)
Endocarditis	5.7 (4.2-7.0)	3.1 (2.2-4.4)
Thromboembolism	17.4 (16.1-22.4)	10.2 (8.7-13.3)
Valve thrombosis	1.1 (0.5-2.0)	0.5 (0.2-1.2)
Bleeding	7.4 (5.6-8.9)	4.5 (2.9-5.6)
Re-intervention	8.8 (6.5-11.3)	4.2 (3.0-5.9)

Results presented as mean with 95% credible interval derived from probabilistic sensitivity analysis in the parentheses.
*Life expectancy of the age- and sex-matched general population was 10.2 for 75-year old patients and 5.6 in 85-year old patients.

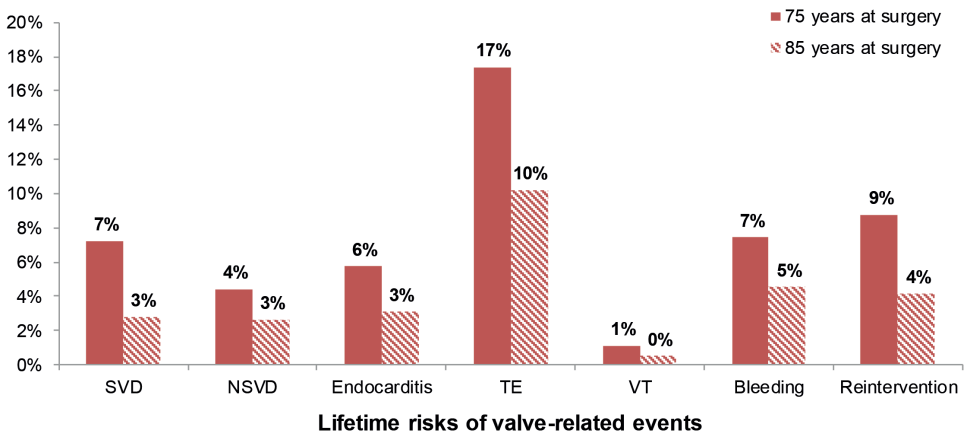


Figure 4. Microsimulation-based age-specific lifetime risks of valve-related morbidity after bioprosthetic aortic valve replacement for patients 75 or 85 years old at the time of surgery.
SVD: structural valve deterioration. NSVD: non-structural valve dysfunction. TE: thromboembolism. VT: valve thrombosis.

Sensitivity analyses

Sensitivity analyses showed that potential publication bias did not substantially influence our pooled outcomes, as they remained largely unchanged after temporary exclusion of the quartile with the smallest sample size (before vs after exclusion: early mortality [5.42% vs. 5.32%], late mortality [5.43%/year vs 5.39%/year], valve-related re-intervention [0.56%/year vs 0.56%/year], SVD [0.42% vs 0.41%], TE [1.83%/year vs 1.78%%/year], and bleeding [0.75%/year vs 0.69%/year]).

Heterogeneity

There was substantial heterogeneity in the following outcome measures (Table 1): early mortality, atrial fibrillation (AF), renal failure, and late SVD, non-structural valve dysfunction (NSVD), TE, bleeding, stroke, and mortality. Univariable random effects meta-regression of bioprostheses studies (Table S8) showed that studies with a greater mean age reported greater early mortality risks.

Studies with a more recent implantation period and studies with a shorter mean follow-up duration reported greater rates of late NSVD after bioprosthetic AVR (moderate correlation between implantation period and mean follow-up duration r = -0.44). Studies with a greater proportion of males reported greater NSVD rates. Studies with a greater proportion of aortic stenosis, as opposed to aortic insufficiency, reported greater TE/stroke rates. However, these patients were also relatively old (moderate correlation between proportion aortic stenosis and mean age: r = 0.57). Studies with a greater mean follow-up duration reported less bleedings. Studies with a greater

mean age or larger proportion of AS, as opposed to AI, reported greater late mortality rates. Studies with a greater proportion of porcine valves compared to pericardial valves reported greater early mortality risks and lower late mortality rates. None of the covariates could explain the heterogeneity in early renal failure risks, late SVD and re-intervention.

DISCUSSION

This study summarized the reported contemporary outcomes after surgical AVR with bioprostheses in elderly patients in the current era in a comprehensive systematic review and meta-analysis combined with extrapolation of results to age-specific life expectancy and lifetime risks using a microsimulation model. The results of this study can inform patients and clinicians about the expected outcomes after bioprosthetic AVR and thereby support treatment decision-making. The translation of the mortality and event rates to life expectancy and lifetime risks allows for better understanding by patients of the associated risks of bioprosthetic AVR. In addition, our results can be used as a benchmark for long-term outcomes after TAVI in patients who were eligible for surgery once they become available. Furthermore, we will use the results of this study to estimate the potential cost-effectiveness of new alternative interventions for conventional surgical AVR (such as in situ tissue-engineered heart valves).

Mortality

In line with previous research, microsimulation revealed that, despite the early mortality risk, life expectancy after bioprosthetic AVR in elderly patients is comparable to the general population.[16] Careful selection of relatively healthy elderly to undergo AVR, whereas frail elderly patients are rejected for surgery, might explain this finding. This also explains why we found a decreased background mortality in patients compared to the age- and sex- matched general population (i.e. hazard ratios for excess mortality <1). The existence of this selection bias is also reflected in lower healthcare costs of nursing homes in elderly patients after surgical valve replacement compared with the general population.[17]

Prosthetic valve dysfunction, endocarditis and re-intervention

The main disadvantage of bioprostheses is that they are subject to valve degeneration over time. Bioprostheses are known to exhibit lower SVD rates with increasing patient age.[13, 18, 19] This is reflected in the SVD rate of 0.42%/year, which is considerably lower than previously reported for young adults (1.59%/year).[20] Our microsimulation results show that 8% of 75-year old patients and 3% of 85-year old patients who received a bioprosthesis developed SVD. Subsequently, re-intervention rates in these

patients were low (0.56%/year vs 1.82%/year in young adults).[20] Besides the lower incidence of SVD, these low re-intervention rates may also reflect less-diligent follow-up or contraindications to perform surgical re-interventions in older compared to younger patients.[21] However, the mortality risk after reoperation has significantly decreased over the past decade.[22, 23] Furthermore, valve-in-valve TAVI is emerging as a less-invasive option for re-intervention of failing bioprostheses.[24]

Bleeding, thromboembolism and valve thrombosis

Although bioprostheses do not require lifelong anticoagulation treatment, we found a greater occurrence of bleedings than in the general population (0.75%/year vs 0.14%/year).[25] This may be explained by early bleedings that occur during the first 3 postoperative months during which anticoagulants are often prescribed.[3, 4] This is supported by our finding that studies with a shorter follow-up reported greater bleeding rates, suggesting the bleedings occur relatively early during follow-up. The greater bleeding rate may also be due to other indications for anticoagulation, such as atrial fibrillation, arising during follow-up in these patients.

TE was the most frequently occurring valve-related event. This TE rate is close to the occurrence rate in the age- and sex-matched general population (1.50%/year).[25] This suggests that factors other than heart valve disease (such as increasing incidence of atherosclerotic disease with age) may have a larger influence on the risk of TE in elderly patients.[26]

The occurrence of valve thrombosis was only reported in 3 studies, but appears to be very low.

Prosthetic valve selection

In prosthetic valve selection, the risk of SVD and subsequent re-intervention associated with bioprostheses is generally weighed against TE and bleeding risk associated with mechanical prostheses. The clinical guidelines recommend bioprostheses in elderly patients requiring AVR.[3, 4] The main reason is that elderly patients are not likely to outlive their bioprosthesis and therefore would not experience the disadvantages of bioprostheses. Our results support the recommendations to use bioprostheses in elderly patients in need of AVR. We demonstrated that the occurrence of SVD after bioprosthetic AVR in elderly patients is low and that re-intervention is rarely necessary. Even when a re-intervention is necessary, this does not have to be associated with increased operative mortality risks due to the improvements in the safety and outcome of surgical re-intervention and the emergence of less invasive transcatheter valve-in-valve replacement for this age group.

Within bioprostheses, one can choose porcine or pericardial valves. In contrast to previous studies, our meta-regression analysis did not reflect prolonged freedom from SVD in pericardial compared to porcine valves.[27] However, the majority of the included studies was not designed to determine differences between valve types.

SAVR versus TAVI

TAVI has emerged as an alternative to surgical AVR in recent years, especially in elderly patients who are often inoperable or at high operable risk.[28, 29] In addition, two large randomized clinical trials have shown that TAVI is noninferior to surgical AVR in intermediate surgical risk patients regarding mortality and disabling strokes.[30, 31] Our study can be used as a benchmark for the long-term outcomes after TAVI in intermediate surgical risk patients once they become available. Although TAVI is a less-invasive procedure than surgical AVR, there are also disadvantages such as the higher occurrence of paravalvular regurgitation, permanent pacemaker requirement, strokes, subclinical valve thrombosis, and vascular and access site-related complications.[32] According to the clinical guidelines, the decision between surgical AVR and TAVI in elderly patients should be made by a heart team (i.e. multidisciplinary group of healthcare professionals) according to the individual patient characteristics, procedural risks, values, and preferences.[3, 4]

Limitations

First, inherent limitations of meta-analyses and combining data from (retrospective) observational studies should be taken into consideration.[33] Second, selection bias of patients included in the studies might have influenced the study outcomes due to the nature of observational studies (i.e. no randomized allocation of patients to treatment options). Third, the presence of publication bias was not investigated with funnel plots, as assessment of publication bias in absolute risk outcomes (as are all of our outcomes) is associated with substantial methodological limitations which may in itself give rise to funnel plot asymmetry.[34] Instead, we conducted sensitivity analyses where the quartile of studies with the smallest sample size was temporarily excluded. Fourth, there was substantial heterogeneity between studies in most outcome measures, which may potentially lead to inaccurate results. However, possible sources of heterogeneity were examined using univariable random effects meta-regression analysis and several covariates that may explain the heterogeneity between studies in the outcome measures were identified. Fifth, because most of the included studies originated from Europe and the United States, the results are less generalizable to patients from other regions in the world. Finally, there are limitations to the microsimulation model that should be taken in to account. The relationship between valve-related events rates after AVR and age, sex, follow-up duration and history of valve-related events remains poorly defined and could, thus, not be

incorporated into our model. The model requires assumptions about the evolution of event occurrence rates and the hazard ratio for excess mortality beyond the observed follow-up period, which has introduced uncertainty in the extrapolation of these events.

Conclusion

Our results support the recommendation to use bioprostheses in elderly patients in need of AVR, since it is associated with low risks of SVD and re-intervention. The estimated life expectancy after bioprosthetic AVR was comparable with the general population. The results of this study can be used to inform patients facing AVR on the risks and benefits of surgical bioprosthetic AVR and they can serve as a benchmark for the long-term outcomes after TAVI in patients who were eligible for surgery and future alternative treatments (e.g. tissue-engineered heart valves). Patients who are facing AVR should be fully informed about the risks and benefits of all treatment options in a shared decision-making process.

Acknowledgements. We thank Wichor Bramer, information specialist at the Medical Library of the Erasmus University Medical Center, for his help with drafting the search query and executing the systematic literature retrieval. We thank Pepijn Grashuis for his help with estimating the hazard ratio for excess mortality.

Funding. This work was supported by the Netherlands Cardio Vascular Research Initiative: The Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences.

Conflicts of interest. None.

REFERENCES

1. Nkomo, V.T., et al., *Burden of valvular heart diseases: a population-based study.* The Lancet, 2006. **368**(9540): p. 1005-1011.
2. Yacoub, M.H. and J.J.M. Takkenberg, *Will heart valve tissue engineering change the world?* Nat Clin Pract Cardiovasc Med, 2005. **2**(2): p. 60-61.
3. Baumgartner, H., et al., *2017 ESC/EACTS Guidelines for the management of valvular heart disease.* European heart journal, 2017. **38**(36): p. 2739-2791.
4. Nishimura, R.A., et al., *2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines.* Circulation, 2017. **135**(25): p. e1159-e1195.
5. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* Annals of internal medicine, 2009. **151**(4): p. W-65-W-94.
6. Akins, C.W., et al., *Guidelines for reporting mortality and morbidity after cardiac valve interventions.* European Journal of Cardio-Thoracic Surgery, 2008. **33**(4): p. 523-528.
7. Borenstein, M., et al., *A basic introduction to fixed-effect and random-effects models for meta-analysis.* Research Synthesis Methods, 2010. **1**(2): p. 97-111.
8. Guyot, P., et al., *Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves.* BMC medical research methodology, 2012. **12**(1): p. 9.
9. Huygens, S.A., et al., *Conceptual model for early health technology assessment of current and novel heart valve interventions.* Open Heart, 2016. **3**(2): p. e000500.
10. van Geldorp, M.W.A., et al., *Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk.* J Thorac Cardiovasc Surg, 2009. **137**(4): p. 881-886. e5.
11. World Health Organization (WHO). *Global Health Observatory data repository - Life tables*. 2016 [cited 2017 7 April]; Available from: http://apps.who.int/gho/data/node.main.687?lang=en.
12. Robert N. Anderson, *United States Life Tables, 1998.* NSVR, 2001. **48**(18): p. 39.
13. Nishida, T., et al., *Long-term results of aortic valve replacement with mechanical prosthesis or carpentier-edwards perimount bioprosthesis in Japanese patients according to age.* Circ J, 2014. **78**(11): p. 2688-2695.
14. Varadarajan, P., et al., *Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: results from a cohort of 277 patients aged≥ 80 years* . European Journal of Cardio-thoracic Surgery, 2006. **30**(5): p. 722-727.
15. Arias, E., *United States Life Tables, 2001.* National Vital Statistics Reports, 2004. **52**(14): p. 39.
16. Kvidal, P., et al., *Observed and relative survival after aortic valve replacement.* Journal of the American College of Cardiology, 2000. **35**(3): p. 747-756.
17. Huygens, S.A., et al., *How much does a heart valve implantation cost and what are the health care costs afterwards?* Open Heart, 2018. **5**(1).

18. Chan, V., et al., *Reoperation of left heart valve bioprostheses according to age at implantation.* Circulation, 2011. **124**(11 suppl 1): p. S75-S80.
19. Rodriguez-Gabella, T., et al., *Aortic Bioprosthetic valve durability: incidence, mechanisms, predictors, and management of surgical and transcatheter valve degeneration.* Journal of the American College of Cardiology, 2017. **70**(8): p. 1013-1028.
20. Etnel, J.R.G., et al. *Outcome after bioprosthetic aortic valve replacement in young adults: a systematic review, meta-analysis and microsimulation*. in *Heart Valve Society 2018 Annual Scientific Meeting* 2018. New York.
21. Sidhu, P., et al., *Mechanical or bioprosthetic valves in the elderly: A 20-year comparison.* Ann Thorac Surg, 2001. **71**(5): p. S257-S260.
22. Davierwala, P.M., et al., *Reoperation is not an independent predictor of mortality during aortic valve surgery.* J Thorac Cardiovasc Surg, 2006. **131**(2): p. 329-335. e2.
23. Maganti, M., et al., *Redo valvular surgery in elderly patients.* Ann Thorac Surg, 2009. **87**(2): p. 521-525.
24. Dvir, D., et al., *Valve-in-Valve International Data Registry Investigators.* Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA, 2014. **312**: p. 162-170.
25. Rothwell, P., et al., *Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study)*. The Lancet, 2005. **366**(9499): p. 1773-1783.
26. De Feo, M., et al., *Mechanical valve prosthesis is a valid option for aortic valve replacement in the elderly.* J Heart Valve Dis, 2004. **13**(1): p. 103-108.
27. Gao, G., et al., *Durability of pericardial versus porcine aortic valves.* J Am Coll Cardiol, 2004. **44**(2): p. 384-388.
28. Leon, M.B., et al., *Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery.* New England Journal of Medicine, 2010. **363**(17): p. 1597-1607.
29. Smith, C.R., et al., *Transcatheter versus surgical aortic-valve replacement in high-risk patients.* New England Journal of Medicine, 2011. **364**(23): p. 2187-2198.
30. Leon, M.B., et al., *Transcatheter or surgical aortic-valve replacement in intermediate-risk patients.* N Engl J Med, 2016. **2016**(374): p. 1609-1620.
31. Reardon, M.J., et al., *Surgical or transcatheter aortic-valve replacement in intermediate-risk patients.* New England Journal of Medicine, 2017.
32. Durko, A.P., R.L. Osnabrugge, and A.P. Kappetein, *Long-term outlook for transcatheter aortic valve replacement*. Trends in cardiovascular medicine, 2017.
33. Ioannidis, J.P. and J. Lau, *Pooling research results: benefits and limitations of meta-analysis.* The Joint Commission journal on quality improvement, 1999. **25**(9): p. 462-469.
34. Sterne, J.A. and M. Egger, *Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis.* J Clin Epidemiol, 2001. **54**(10): p. 1046-55.

SUPPLEMENTAL MATERIAL

Search terms

Embase.com

('aorta valve replacement'/de OR 'aorta valve prosthesis'/de OR ('heart valve prosthesis'/de AND 'aorta valve'/de) OR (aort* AND (valve*) NEAR/6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent*)):ab,ti) AND (xenograft/de OR (xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR 'Carpentier-Edwards' OR Shiley OR hancock) NEAR/6 (graft* OR transplant* OR prosthe* OR bioprosthe* OR valve* OR aort*))):ab,ti) OR ('heart valve bioprosthesis'/de OR 'Carpentier Edwards bioprosthesis'/de OR 'Hancock valve prosthesis'/de OR 'Mosaic bioprosthesis'/de OR (('Carpentier-Edwards' OR Shiley OR hancock OR freestyle* OR mosaic OR '3f enable' OR biocor OR 'toronto spv') NEAR/6 (valve* OR bioprosthe* OR prosthe*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND ('clinical study'/de OR 'case control study'/exp OR 'clinical article'/de OR 'clinical trial'/exp OR 'intervention study'/de OR 'longitudinal study'/exp OR 'major clinical study'/de OR 'prospective study'/de OR 'retrospective study'/de OR mortality/de OR 'cardiovascular mortality'/de OR 'surgical mortality'/de OR 'treatment outcome'/exp OR survival/exp OR 'graft survival'/de OR 'quality of life'/de OR 'follow up'/de OR 'evaluation study'/de OR 'comparative effectiveness'/de OR reoperation/de OR (clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality NEAR/3 life) OR result* OR (follow* NEXT/1 up*) OR 'long-term' OR longterm OR death OR evaluat* OR effectiv* OR reoperat*):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Conference Paper]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim OR [Conference Review]/lim)

Medline (OvidSP)

(("heart valve prosthesis"/ AND "aortic valve"/) OR (aort* ADJ6 (valve*) ADJ6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent*)).ab,ti.) AND (heterografts/ OR (xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR "Carpentier-Edwards" OR Shiley OR hancock) ADJ6 (graft* OR transplant* OR prosthe* OR bioprosthe* OR valve* OR aort*))).ab,ti.) OR ((("Carpentier-Edwards" OR Shiley OR hancock OR freestyle* OR mosaic OR "3f enable" OR biocor OR "toronto spv") ADJ3 (valve* OR bioprosthe* OR prosthe*)).ab,ti.) NOT (exp animals/ NOT humans/) AND ("Clinical Trial".pt. OR exp "Case-Control Studies"/ OR "Intervention Studies"/ OR exp "Longitudinal Studies"/ OR exp mortality/ OR mortality.xs. OR exp "treatment outcome"/ OR survival/ OR "graft survival"/ OR "quality of life"/ OR (clinical* OR trial*

OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality ADJ3 life) OR result* OR (follow* ADJ up*) OR "long-term" OR longterm OR death OR evaluat* OR effectiv* OR reoperat*).ab,ti.) AND english.la. NOT (congresses OR Letters OR Notes OR Editorials).pt.

Cochrane

((aort* AND (valve*) NEAR/6 (replace* OR transplant* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent*)):ab,ti) AND ((xenograft* OR xenotransplant* OR heterograft* OR heterotransplant* OR ((xeno* OR hetero* OR porcine* OR swine OR pig OR bovine* OR nonhuman OR animal OR calf OR cow OR 'Carpentier-Edwards' OR Shiley OR hancock) NEAR/6 (graft* OR transplant* OR prosthe* OR bioprosthe* OR valve* OR aort*))):ab,ti) OR (((('Carpentier-Edwards' OR Shiley OR hancock OR freestyle* OR mosaic OR '3f enable' OR biocor OR 'toronto spv') NEAR/3 (valve* OR bioprosthe* OR prosthe*)):ab,ti) AND ((clinical* OR trial* OR prospect* OR retrospect* OR longitudin* OR mortali* OR outcome* OR failure* OR surviv* OR (quality NEAR/3 life) OR result* OR (follow* NEXT/1 up*) OR 'long-term' OR longterm OR death OR evaluat* OR effectiv* OR reoperat*):ab,ti)

PubMed publisher

(("heart valve prosthesis"[mh] AND "aortic valve"[mh]) OR (aorta valve*[tiab] OR aortic valve*[tiab]) AND (replace*[tiab] OR transplant*[tiab] OR xenotransplant*[tiab] OR xenograft*[tiab] OR heterotransplant*[tiab] OR heterograft*[tiab] OR prosthe*[tiab] OR bioprosthe*[tiab] OR stent*[tiab]))) AND (heterografts[mh] OR (xenograft*[tiab] OR xenotransplant*[tiab] OR heterograft*[tiab] OR heterotransplant*[tiab] OR ((xeno*[tiab] OR hetero*[tiab] OR porcine*[tiab] OR swine[tiab] OR pig[tiab] OR bovine*[tiab] OR nonhuman[tiab] OR animal[tiab] OR calf[tiab] OR cow[tiab] OR Carpentier-Edwards[tiab] OR Shiley[tiab] OR hancock[tiab]) AND (graft*[tiab] OR transplant*[tiab] OR prosthe*[tiab] OR bioprosthe*[tiab] OR valve*[tiab] OR aort*[tiab])))) OR (((Carpentier-Edwards[tiab] OR Shiley[tiab] OR hancock[tiab] OR freestyle*[tiab] OR mosaic[tiab] OR 3f enable*[tiab] OR biocor[tiab] OR toronto spv*[tiab]) AND (valve*[tiab] OR bioprosthe*[tiab] OR prosthe*[tiab]))) NOT (animals[mh] NOT humans[mh]) AND ("Clinical Trial".pt. OR "Case-Control Studies"[mh] OR "Intervention Studies"[mh] OR "Longitudinal Studies"[mh] OR mortality[mh] OR mortality[sh] OR "treatment outcome"[mh] OR survival[mh] OR "graft survival"[mh] OR "quality of life"[mh] OR (clinical*[tiab] OR trial*[tiab] OR prospect*[tiab] OR retrospect*[tiab] OR longitudin*[tiab] OR mortali*[tiab] OR outcome*[tiab] OR failure*[tiab] OR surviv*[tiab] OR quality of life*[tiab] OR result*[tiab] OR follow up*[tiab] OR long-term*[tiab] OR longterm[tiab] OR death OR evaluat* OR effectiv* OR reoperat*[tiab])) AND english[la] AND publisher[sb]

Google scholar
"aorta|aortic valve replacement|prosthesis|transplantation" xenograft|xenotransplantation|heterograft|heterotransplantation|"Carpentier-Edwards"|hancock clinical|trial|intervention|longitudinal|prospective|retrospective|mortality|outcome|survival|follow-up

Embase.com (Embase en Medline)
('Aorta valve replacement'/de OR 'Aorta Valve Prosthesis'/exp OR (('Aorta Valve'/de OR 'Aorta Valve Disease'/exp OR ((aortic OR aorta) NEAR/3 (valve OR valvul* OR stenos* OR insufficien* OR regurgitat* OR incompeten*)):ab,ti) AND ('Transplantation'/de OR 'Implantation'/exp OR (replac* OR transplant* OR implant* OR artificial):ab,ti)) OR (AVR AND valve):ab,ti) AND ('Mechanical heart valve'/exp OR (mechanical OR mechano* OR ATS OR 'Bjork Shiley' OR 'Bjoerk Shiley' OR CarboMedic* OR 'Saint Jude' OR 'St Jude' OR 'St. Jude' OR 'Starr Edwards' OR pyrocarbon OR LTIC OR carbon):ab,ti) AND ('Survival'/exp OR 'Mortality'/exp OR 'Prognosis'/de OR 'Treatment outcome'/exp OR 'Evaluation and follow up'/de OR 'Follow up'/de OR 'Hazard Assessment'/de OR (surviv* OR mortalit* OR death* OR prognos* OR outcome* OR 'follow up' OR 'long term' OR hazard*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OVID)
((("Aortic Valve"/ OR exp "Aortic Valve Stenosis"/ OR "Aortic Valve Insufficiency"/ OR ((aortic OR aorta) ADJ3 (valve OR valvul* OR stenos* OR insufficien* OR regurgitat* OR incompeten*)).ab,ti.) AND ("Transplantation"/ OR transplantation.xs. OR "Heart Valve Prosthesis Implantation"/ OR (replac* OR transplant* OR implant* OR artifical).ab,ti.)) OR (AVR AND valve).ab,ti.) AND ("Carbon"/ OR (mechanical OR mechano* OR ATS OR "Bjork Shiley" OR "Bjoerk Shiley" OR Carbomedic* OR "Saint Jude" OR "St Jude" OR "St. Jude" OR "Starr Edwards" OR pyrocarbon OR LTIC OR carbon).ab,ti.) AND ("Survival"/ OR exp "Mortality"/ OR mortality.xs. OR "Prognosis"/ OR exp "Treatment outcome"/ OR "Follow-Up Studies"/ OR (surviv* OR mortalit* OR death* OR prognos* OR outcome* OR "follow up" OR "long term" OR hazard*).ab,ti.) NOT (animals NOT humans).sh.

Cochrane Central
(((((aortic OR aorta) NEAR/3 (valve OR valvul* OR stenos* OR insufficien* OR regurgitat* OR incompeten*)):ab,ti) AND ((replac* OR transplant* OR implant* OR artificial):ab,ti)) OR (AVR AND valve):ab,ti) AND ((mechanical OR mechano* OR ATS OR 'Bjork Shiley' OR 'Bjoerk Shiley' OR CarboMedic* OR 'Saint Jude' OR 'St Jude' OR 'St. Jude' OR 'Starr Edwards' OR pyrocarbon OR LTIC OR carbon):ab,ti) AND ((surviv* OR mortalit* OR death* OR prognos* OR outcome* OR 'follow up' OR 'long term' OR hazard*):ab,ti)

Web of Science

TS=(((((aortic OR aorta) NEAR/2 (valve OR valvul* OR stenos* OR insufficien* OR regurgitat* OR incompeten*)) AND (replac* OR transplant* OR implant* OR artificial)) OR (AVR AND valve)) AND ((mechanical OR mechano* OR ATS OR "Bjork Shiley" OR "Bjoerk Shiley" OR CarboMedic* OR "Saint Jude" OR "St Jude" OR "St. Jude" OR "Starr Edwards" OR pyrocarbon OR LTIC OR carbon)) AND ((surviv* OR mortalit* OR death* OR prognos* OR outcome* OR "follow up" OR "long term" OR hazard*)) NOT ((animal* OR rat OR rats OR mouse OR mice OR pigs Or swine OR sheep) NOT (human* OR people OR patient*)))

Data extraction

Study characteristics

- Year of publication
- Country or region
- Study design
- Patients (n)
- Implantation period
- Follow-up (mean, SD, total number of patient-years, and completeness)

Patient characteristics

- Age (mean, SD, and range)
- Weight (mean, SD, and range)
- Males (n)
- Emergency procedures (n)
- Preoperative NYHA class (n)
- Hemodynamics: stenosis, regurgitation or combined lesion (n)
- Etiology
    - Congenital (n)
    - Degenerative/calcification (n)
    - Rheumatic (n)
    - Endocarditis (n)
    - Prosthetic valve dysfunction (n)
    - Other/Unknown (n)
- Previous cardiac intervention (n)
    - Aortic valve replacement
    - Aortic valve repair
    - CABG
    - Other/unknown

Surgical details

- Prosthesis
  - Stented
  - Stentless
  - Porcine
  - Pericardial
  - Other

- Concomitant procedures (n)
  - CABG
  - Aortic surgery
  - Other valve repair
  - Other

Early outcome

- Mortality (n)
- Re-intervention (n)
  - Valve-related re-intervention (n)
  - Non-valve related cardiac re-intervention (n)
  - Reexploration for bleeding (n)
- Structural valve deterioration (SVD) (n)
  - Re-intervention (n)
- Non-structural valve dysfunction (NSVD) (n)
  - Re-intervention (n)
- Endocarditis (n)
  - Re-intervention (n)
- Thromboembolism (TE) (n)
  - Re-intervention (n)
- Valve thrombosis (VT) (n)
  - Re-intervention (n)
- TE/VT (n)
  - Re-intervention (n)
- Bleeding (n)
  - Re-intervention (n)
- Cerebrovascular accident (CVA) (stroke+TIA) (n)
  - Thromboembolic (n)
  - Hemorrhagic (n)
- Stroke (n)
  - Thromboembolic (n)
  - Hemorrhagic (n)

- Transient ischemic attack (TIA) (n)
  - Thromboembolic (n)
  - Hemorrhagic (n)
- Myocardial infarction (MI) (n)
  - Re-intervention (n)
- Pacemaker Implantation (n)
  - Re-intervention (n)
- Renal failure (n)
  - Re-intervention (n)

Late outcome

- Mortality (n)
  - Cardiac (n)
    - » Valve related (n)
      - SUD (n)
  - Other (n)
- Re-intervention (n)
  - Valve-related re-intervention (n)
    - » Mortality (n)
  - Non--valve-related cardiac re-intervention (n)
    - » Mortality (n)
- Valve dysfunction (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality
- SVD (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality
- NSVD (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality
- Endocarditis (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality

- TE (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality
- VT (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality
- TE/VT (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality
- Bleeding (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality
- CVA (stroke+TIA) (n)
  - Mortality (n)
  - Thromboembolic (n)
  - Hemorrhagic (n)
- Stroke (n)
  - Mortality (n)
  - Thromboembolic (n)
  - Hemorrhagic (n)
- TIA (n)
  - Mortality (n)
  - Thromboembolic (n)
  - Hemorrhagic (n)
- MI (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality
- Pacemaker Implantation (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality
- Renal failure (n)
  - Mortality (n)
  - Re-intervention (n)
    - » Mortality

Statistical software

Meta-analysis and heterogeneity tests were performed in Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA). Published Kaplan-Meier curves were digitized using Engauge Digitizer (version 10.3, http://markummitchell.github.io/engauge-digitizer). Shapiro-Wilk tests, univariable random effects meta-regression analyses, extrapolation of estimated individual patient time-to-event data from the digitized curves, meta-analysis of the derived Kaplan-Meier curves, and microsimulation were performed in R (version 3.3.2, R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria) using the software RStudio Version 1.0.136 (RStudio, Inc).

References included studies

Accola, K.D., et al., Surgical management of aortic valve disease in the elderly: A retrospective comparative study of valve choice using propensity score analysis. J Heart Valve Dis, 2008. 17(4): p. 355-365.

Ali, A., et al., Are stentless valves superior to modern stented valves? Circulation, 2006. 114(1 suppl): p. I-535-I-540.

Ali, A., et al., Early clinical and hemodynamic outcomes after stented and stentless aortic valve replacement: results from a randomized controlled trial. The Annals of thoracic surgery, 2007. 83(6): p. 2162-2168.

Arinaga, K., et al., Twelve-year experience with the Carpentier–Edwards pericardial aortic valve at a single Japanese center. Journal of Artificial Organs, 2011. 14(3): p. 209-214.

Ashikhmina, E.A., et al., Aortic valve replacement in the elderly determinants of late outcome. Circulation, 2011. 124(9): p. 1070-1078.

Aymard, T., et al., Clinical experience with the second-generation 3f Enable sutureless aortic valve prosthesis. The Journal of thoracic and cardiovascular surgery, 2010. 140(2): p. 313-316.

Bose, A.K., J.D. Aitchison, and J.H. Dark, Aortic valve replacement in octogenarians. Journal of cardiothoracic surgery, 2007. 2(1): p. 33.

Chiappini, B., et al., Clinical outcome of aortic valve replacement in the elderly. Cardiovascular surgery, 2003. 11(5): p. 359-365.

Colli, A., et al., The TRIBECA study: (TRI)fecta (B)ioprosthesis (E)valuation versus (C)arpentier Magna-Ease in (A)ortic position. Eur J Cardio-thorac Surg, 2016. 49(2): p. 478-485.

de Vincentiis, C., et al., Aortic Valve Replacement in Octogenarians: Is Biologic Valve the Unique Solution? Ann Thorac Surg, 2008. 85(4): p. 1296-1301.

Doss, M., et al., Performance of stentless versus stented aortic valve bioprostheses in the elderly patient: a prospective randomized trial. European journal of cardio-thoracic surgery, 2003. 23(3): p. 299-304.

Dunning, J., et al., Stentless vs. stented aortic valve bioprostheses: a prospective randomized controlled trial. European heart journal, 2007. 28(19): p. 2369-2374.

Ennker, J., et al., The Stentless Freestyle Bioprosthesis: Impact of Age Over 80 Years on Quality of Life, Perioperative, and Mid-Term Outcome. Journal of cardiac surgery, 2006. 21(4): p. 379-385.

Filsoufi, F., et al., Excellent early and late outcomes of aortic valve replacement in people aged 80 and older. Journal of the American Geriatrics Society, 2008. 56(2): p. 255-261.

Flameng, W., et al., Effect of sutureless implantation of the Perceval S aortic valve bioprosthesis on intraoperative and early postoperative outcomes. The Journal of thoracic and cardiovascular surgery, 2011. 142(6): p. 1453-1457.

Florath, I., et al., Mid term outcome and quality of life after aortic valve replacement in elderly people: Mechanical versus stentless biological valves. Heart, 2005. 91(8): p. 1023-1029.

Folliguet, T.A., et al., Sutureless perceval aortic valve replacement: results of two European centers. The Annals of thoracic …, 2012.

Gelsomino, S., et al., Stentless aortic valve replacement in elderly patients. Cardiovascular surgery, 2002. 10(3): p. 223-237.

Glaser, N., A. Franco-Cereceda, and U. Sartipy, Late haemodynamic performance and survival after aortic valve replacement with the Mosaic bioprosthesis. Interact Cardiovasc Thorac Surg, 2014. 19(5): p. 756-762.

Hellgren, L., et al., Biological versus mechanical prosthesis in 3279 patients from the Swedish in-patients register. Scandinavian Cardiovascular Journal, 2011. 45(4): p. 223-228.

Kawachi, Y., et al., Aortic valve replacement in patients age 70 years and older: Early and late results. Artif Organs, 2002. 26(8): p. 706-710.

Kurlansky, P.A., et al., Surgical management of aortic valve disease in elderly patients with and without coronary artery disease: influence on quality of life. Journal of Cardiovascular Surgery, 2007. 48(2): p. 215.

Lehmann, S., et al., Mid-Term Results after Epic™ Xenograft Implantation for Aortic, Mitral, and Double Valve Replacement. Journal of heart valve disease, 2007. 16(6): p. 641.

Litmathe, J., et al., Aortic valve replacement in octogenarians:Outcome and predictors of complications. Hell J Cardiol, 2011. 52(3): p. 211-215.

Luciani, G.B., et al., Survival after stentless and stented xenograft aortic valve replacement: a concurrent, controlled trial. The Annals of thoracic surgery, 2002. 74(5): p. 1443-1449.

Martinovic, I., et al., Eight-year results after aortic valve replacement with the CryoLife-O'Brien Stentless Aortic Porcine Bioprosthesis. The Journal of thoracic and cardiovascular surgery, 2005. 130(3): p. 777. e1-777. e7.

Mistiaen, W., et al., Risk factors and survival after aortic valve replacement in octogenarians. Journal of Heart Valve Disease, 2004. 13(4): p. 538-544.

Murashita, T., et al., Aortic valve replacement for severe aortic valve stenosis in the nonagenarian patient. The Annals of thoracic surgery, 2014. 98(5): p. 1593-1597.

Nishida, T., et al., Long-term results of aortic valve replacement with mechanical prosthesis or carpentier-edwards perimount bioprosthesis in Japanese patients according to age. Circ J, 2014. 78(11): p. 2688-2695.

Nishioka, N., et al., Outcomes of surgical aortic valve replacement using Carpentier-Edwards PERIMOUNT bioprosthesis series in elderly patients with severe aortic valve stenosis: a retrospective cohort study. Gen Thorac Cardiovasc Surg, 2016: p. 1-7.

Pavie, A.J., et al., Aortic valve replacement with the composite Labcor procine bioprosthesis in the elderly. Journal of Cardiovascular Surgery, 2001. 42(3): p. 317.

Pavoni, D., et al., Limited long-term durability of the Cryolife O'Brien stentless porcine xenograft valve. Circulation, 2007. 116(11 SUPPL. 1): p. I307-I313.

Permanyer, E., et al., The 3f Enable sutureless bioprosthesis: Early results, safeguards, and pitfalls. J Thorac Cardiovasc Surg, 2014.

Riess, F.C., et al., The Mosaic porcine bioprosthesis: Role of age on clinical performance in aortic position. J Thorac Cardiovasc Surg, 2011. 141(6): p. 1440-1448.

Ruggieri, V.G., et al., Long-term results of the carpentier-edwards supraannular aortic valve prosthesis. Ann Thorac Surg, 2012. 94(4): p. 1191-1197.

Said, S.M., et al., Do pericardial bioprostheses improve outcome of elderly patients undergoing aortic valve replacement? Ann Thorac Surg, 2012. 93(6): p. 1868-1875.

Sidhu, P., et al., Mechanical or bioprosthetic valves in the elderly: A 20-year comparison. Ann Thorac Surg, 2001. 71(5): p. S257-S260.

Sjogren, J., T. Gudbjartsson, and L.I. Thulin, Long-term outcome of the Mitroflow pericardial bioprosthesis in the elderly after aortic valve replacement. Journal of Heart Valve Disease, 2006. 15(2): p. 197.

Suttie, S.A., et al., Elderly valve replacement with bioprostheses and mechanical prostheses. Comparison by composites of complications. J Cardiovasc Surg, 2006. 47(2): p. 191-199.

Varadarajan, P., et al., Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: results from a cohort of 277 patients aged≥ 80 years . European Journal of Cardio-thoracic Surgery, 2006. 30(5): p. 722-727.

Vicchio, M., et al., Tissue versus mechanical prostheses: quality of life in octogenarians. Ann Thorac Surg, 2008. 85(4): p. 1290-1295.

Walczak, A., et al., Early results of aortic valve replacement with Labcor biological prostheses. Emergency, 2008. 7(08): p. 4-24.

Table S1. Overview of included publications on bioprostheses

First author	Implantation period	No. of patients	Study type	Mean follow-up, years (SD)	Mean age, years (range)	Male, n (%)	Concomitant CABG, n (%)	Emergency surgery, n (%)	Preoperative NYHA class III/IV, n (%)	Aortic stenosis, n (%)
Accola	1989-2003	398	Retrospective	6.3 (-)	74.5 (65.0-89.0)	268 (67.3)	219 (55.0)	2 (0.5)	278 (69.8)	137 (34.4)
Ali 2007	2001-2004	161	Prospective	-	75.5 (65.0--)	79 (49.1)	59 (36.6)	0 (0.0)	-	- ()
Ali 2006	2001-2004	161	Prospective	1.9 (0.9)	75.5 (65.0--)	79 (49.1)	-	0 (0.0)	-	- ()
Arinaga	1996-2007	244	Retropective	4.1 (-)	71.6 (65.0--)	113 (46.3)	31 (12.7)	-	-	135 (55.3)
Ashikhmina*	1993-2007	2658	Retrospective	5.0 (3.5)	78.0 (70.0--)	1659 (62.4)	1396 (52.5)	14 (0.5)	1947 (73.3)	- ()
Aymard	-	28	Prospective	-	75.7 (72.0-89.0)	10 (35.7)	-	-	28 (100.0)	- ()
Bose*	2001-2004	68	Retrospective	1.9 (-)	83.1 (80.0--)	38 (55.9)	31 (45.6)	18 (26.5)	34 (50.0)	- ()
Chiappini	1993-2000	166	Retrospective	-	- (70.0-89.0)	-	-	-	-	- ()
Colli	2011-2013	791	Retrospective	-	75.2 (67.0-80.0)	421 (53.2)	177 (22.4)	18 (2.3)	420 (53.1)	652 (82.4)
de Vincentiis	1991-2005	200	Retrospective	3.3 (2.8)	82.0 (80.0-92.0)	89 (44.5)	78 (39.0)	5 (2.5)	173 (86.5)	- ()
Doss	1999-2001	40	Prospective	-	78.5 (75.0--)	19 (47.5)	5 (12.5)	0 (0.0)	35 (87.5)	- ()
Dunning	2002-2004	60	Prospective	-	73.0 (65.0-0.0)	37 (61.7)	-	0 (0.0)	29 (48.3)	56 (93.3)
Ennker*	1996-2002	76	Retrospective	2.7 (1.8)	82.0 (80.0--)	21 (28.0)	-	-	44 (58.0)	- ()
Filsoufi	1998-2006	231	Retrospective	-	83.0 (80.0--)	94 (40.7)	110 (47.6)	5 (2.2)	113 (48.9)	- ()
Flameng	2007-2009	32	Retrospective	1.3 (-)	78.0 (75.0-87.0)	14 (45.0)	62 (193.8)	-	32 (100.0)	32 (100.0)
Florath	1996-2001	247	Retrospective	2.5 (1.5)	76.0 (65.0--)	124 (50.0)	104 (42.0)	3 (1.2)	148 (60.0)	- ()
Folliguet*	2007-2011	208	Prospective	0.8 (1.0)	79.0 (65.0--)	67 (32.2)	44 (21.2)	0 (0.0)	208 (100.0)	- ()
Gelsomino	1993-2000	36	Retrospective	3.1 (1.0)	78.1 (75.0--)	18 (50.0)	13 (36.1)	0 (0.0)	35 (97.2)	24 (66.7)
Glaser*	2002-2008	355	Retrospective	7.1 (-)	75.7 (---)	192 (54.1)	-	4 (1.0)	-	298 (84.0)
Hellgren	1985-2003	1031	Retrospective	4.9 (-)	- (70.0--)	-	-	-	-	- ()
Kawachi	1994-2001	28	Retrospective	2.9 (2.0)	76.0 (70.0-88.0)	15 (53.6)	-	4 (14.3)	-	16 (57.1)
Kurlansky	1976-1999	866	Retrospective	4.8 (-)	77.6 (65.0-93.0)	530 (61.2)	-	-	-	505 (58.3)
Lehmann*	2001-2006	1168	Prospective	1.8 (1.3)	76.0 (70.0--)	580 (49.7)	515 (44.1)	-	-	767 (65.7)
Litmathe	1998-2008	152	Retrospective	-	82.6 (70.0--)	97 (64.0)	-	88 (58.1)	-	- ()

Table S1. Continued

First author	Implantation period	No. of patients	Study type	Mean follow-up, years (SD)	Mean age, years (range)	Male, n (%)	Concomitant CABG, n (%)	Emergency surgery, n (%)	Preoperative NYHA class III/IV, n (%)	Aortic stenosis, n (%)
Luciani*	1992-2000	668	Retrospective	3.4 (2.7)	72.2 (65.0--)	341 (51.0)	186 (27.8)	-	542 (81.1)	443 (66.3)
Martinovic	1996-2004	206	Prospective	4.7 (-)	72.8 (65.0-84.0)	89 (43.2)	76 (36.9)	-	168 (81.6)	62 (30.1)
Mistiaen*	1986-2000	60	Retrospective	4.0§ (-)	- (80.0--)	22 (36.7)	-	5 (8.3)	-	- ()
Murashita	1993-2013	33	Retrospective	-	91.0 (90.0-97.0)	12 (36.4)	-	2 (6.1)	0 (0.0)	33 (100.0)
Nishida*	1981-2013	199	Retrospective	4.6 (0.3)	76.6 (0.0-0.0)	111 (55.8)	42 (21.1)	-	-	- ()
Nishioka*	2001-2013	136	Retrospective	3.8 (3.0)	76.6 (65.0-88.0)	47 (34.6)	-	-	-	- ()
Pavie	1988-1995	100	Retrospective	2.7 (-)	80.0 (70.0-90.0)	37 (37.0)	26 (26.0)	-	72 (72.0)	100 (100.0)
Pavoni*	1994-2004	185	Retrospective	5.3 (3.4)	72.0 (65.0--)	82 (44.3)	51 (27.6)	0 (0.0)	127 (68.6)	78 (42.2)
Permanyer*	2011-2014	60	Prospective	-	81.3 (70.0-92.0)	32 (53.3)	23 (38.3)	-	42 (70.0)	42 (70.0)
Riess	1994-1999	167	Prospective	7.9§ (-)	72.0 (66.0-82.0)	84 (50.3)	69 (41.3)	-	118 (70.7)	29 (17.4)
Ruggieri	1983-1994	714	Prospective	13.7 (6.6)†	- (70.0--)	-	-	-	-	- ()
Said	1993-2007	2979	Retrospective	5.2 (3.2)	77.0 (65.0--)	1878 (63.0)	1550 (52.0)	16 (0.5)	2161 (72.5)	- ()
Sidhu	1977-1997	249	Retrospective	4.1 (-)	74.5 (70.0-90.0)‡	138 (55.4)	-	-	-	- ()
Sjogren	1990-1993	152	Retrospective	6.2 (3.2)	79.5 (75.0-91.0)	60 (39.5)	74 (48.7)	6 (3.9)	118 (77.6)	126 (82.9)
Suttie	1975-1999	616	Retrospective	4.1 (-)	78.9 (75.0-94.6)‡	363 (58.9)	316 (51.3)	-	-	522 (84.7)
Varadarajan*	1993-2003	80	Retrospective	2.5 (-)	83.0 (---)	46 (57.0)	37 (46.3)	-	-	80 (100.0)
Vicchio*	1992-2006	68	Retrospective	3.4 (2.8)	82.9 (80.0-90.0)	31 (45.6)	15 (22.0)	-	50 (73.6)	- ()
Walczak	2006-2008	36	Retrospective	-	72.2 (65.0-80.0)	21 (58.3)	10 (27.8)	2 (5.6)	28 (77.8)	27 (75.0)

95% confidence interval provided in parentheses. SD: standard deviation. CABG: Coronary artery bypass grafting. NYHA: New York Heart Association. *Included in pooled Kaplan-Meier survival curve. "-": variable not reported. †Based on total population instead of subgroup of elderly patients. ‡Based on total population instead of subgroup of patients after bioprosthetic AVR. §: median

Table S2. Probabilities of dying and re-intervention after valve-related events used in the microsimulation model.

Event	Probability of dying	Probability of re-intervention	Source of the probabilities (probability of dying; re-intervention)
Structural valve deterioration	0.17	0.43	van Geldorp et al. 2009†; this meta-analysis (reported in 7 of the included studies)
Non-structural valve dysfunction	0.05	0.39	van Geldorp et al. 2009†; this meta-analysis (reported in 4 of the included studies)
Endocarditis	0.34	0.49	van Geldorp et al. 2009†; this meta-analysis (reported in 7 of the included studies)
Thromboembolism	0.33	0	van Geldorp et al. 2009†; assumption
Valve thrombosis	0	1	van Geldorp et al. 2009†
Bleeding	0.39	0	This meta-analysis (reported in 4 of the included studies); assumption
Re-intervention (HR)*	2.7		This meta-analysis (reported in 4 of the included studies)

*Hazard ratio applied to early mortality risk. †van Geldorp MWA, Eric Jamieson WR, Kappetein AP, et al. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk. J. Thorac. Cardiovasc. Surg. 2009;137:881-886. e885.

Table S3. Individual study outcome estimates of early mortality and valve-related events after bioprosthetic AVR

First author	Early mortality	Reexploration for bleeding	Early stroke	Early MI	Early renal failure
Accola	4.02 (2.49-6.50)	3.77 (2.29-6.19)	-	0.50 (0.13-2.00)	8.04 (5.77-11.21)
Ali 2007	3.11 (1.31-7.36)	5.59 (2.96-10.55)	-	0.62 (0.09-4.38)	-
Ali 2006	-	-	-	-	-
Arinaga	2.05 (0.86-4.88)	-	-	-	-
Ashikhmina	-	-	-	-	-
Aymard	7.14 (1.88-27.16)	-	-	-	-
Bose	13.00 (7.03-24.04)	4.41 (1.46-13.34)	1.47 (0.21-10.29)	-	10.29 (5.10-20.76)
Chiappini	7.23 (4.19-12.47)	-	-	-	-
Colli	3.03 (2.05-4.50)	-	-	-	-
de Vincentiis	8.50 (5.39-13.39)	2.00 (0.76-5.28)	-	-	4.00 (2.03-7.89)
Doss	5.00 (1.30-19.30)	-	-	-	-
Dunning	1.67 (0.24-11.64)	-	-	-	-
Ennker	6.58 (2.82-15.35)	-	-	-	-
Filsoufi	5.19 (2.99-9.01)	2.16 (0.91-5.15)	3.90 (2.05-7.39)	0.87 (0.22-3.44)	0.87 (0.22-3.44)
Flameng	1.56 (0.10-24.44)	3.13 (0.45-21.51)	-	-	-
Florath	-	-	-	-	-
Folliguet	2.40 (1.01-5.71)	-	-	-	-
Gelsomino	-	2.78 (0.40-19.19)	-	-	-
Glaser	4.80 (3.02-7.63)	-	-	-	-
Hellgren	-	-	-	-	-
Kawachi	1.79 (0.11-27.85)	-	-	-	-
Kurlansky	7.51 (5.94-9.48)	3.70 (2.63-5.19)	-	0.69 (0.31-1.54)	9.35 (7.60-11.51)
Lehmann	8.00 (6.59-9.72)	-	-	-	-
Litmathe	6.20 (3.34-11.51)	5.70 (2.99-10.88)	-	-	6.40 (3.48-11.75)
Luciani	4.19 (2.92-6.02)	-	-	-	-
Martinovic	4.80 (2.61-8.82)	1.94 (0.74-5.12)	-	-	-
Mistiaen	10.00 (4.68-21.36)	-	-	3.33 (0.85-13.02)	-
Murashita	-	-	1.52 (0.10-23.72)	1.52 (0.10-23.72)	18.18 (8.82-37.49)
Nishioka	0.37 (0.02-5.85)	-	2.21 (0.72-6.75)	-	0.74 (0.10-5.18)
Pavie	15.00 (9.41-23.92)	-	-	-	-
Pavoni	5.40 (2.95-9.87)	-	-	-	-
Permanyer	6.67 (2.59-17.18)	3.33 (0.85-13.02)	3.33 (0.85-13.02)	-	6.67 (2.59-17.18)
Riess	1.80 (0.59-5.51)	-	0.60 (0.08-4.23)	-	-
Ruggieri	-	-	-	-	-
Said	4.06 (3.41-4.84)	5.40 (4.65-6.28)	-	-	-
Sidhu	2.01 (0.84-4.78)	-	-	-	-
Sjogren	2.63 (1.00-6.92)	-	-	-	-
Suttie	9.25 (7.23-11.85)	-	-	-	-
Vicchio	10.29 (5.10-20.76)	-	1.47 (0.21-10.29)	-	-
Walczak	8.33 (2.82-24.62)	8.33 (2.82-24.62)	2.78 (0.40-19.19)	-	2.78 (0.40-19.19)

Results presented as percentages with 95% confidence interval provided in parentheses. MI: Myocardial infarction.

Table S4. Individual study outcome estimates of late mortality after bioprosthetic AVR

First author	Late mortality (%/year)	Cardiac late mortality (%/year)	Valve-related late mortality (%/year)	SUD (%/year)
Accola	7.86 (6.87-8.98)	-	-	-
Ali 2007	-	-	-	-
Ali 2006	2.88 (1.51-5.49)	-	-	-
Arinaga	2.89 (2.00-4.20)	-	1.07 (0.04-0.14)	0.21 (0.05-0.86)
Ashikhmina	9.66 (9.17-10.18)	-	-	-
Aymard	-	-	-	-
Bose	-	-	-	-
Chiappini	-	-	-	-
Colli	-	-	-	-
de Vincentiis	-	-	-	-
Doss	-	-	-	-
Dunning	-	-	-	-
Ennker	1.53 (1.01-2.31)	-	-	-
Filsoufi	-	-	-	-
Flameng	7.12 (2.39-21.19)	-	-	-
Florath	-	-	-	-
Folliguet	12.82 (8.52-19.30)	-	-	-
Gelsomino	-	-	-	-
Glaser	7.49 (6.53-8.59)	1.59 (1.17-2.16)	-	-
Hellgren	-	-	-	-
Kawachi	3.69 (1.22-11.22)	0.62 (0.04-9.76)	0.62 (0.07-18.81)	0.62 (0.04-9.76)
Kurlansky	9.79 (8.89-10.78)	-	-	-
Lehmann	5.16 (4.30-6.20)	2.51 (1.92-3.27)	-	-
Litmathe	-	-	-	-
Luciani	2.94 (2.32-3.72)	1.82 (1.35-2.47)	-	-
Martinovic	1.25 (0.71-2.19)	0.42 (0.16-1.11)	0.10 (0.06-2.92)	0.10 (0.01-0.74)
Mistiaen	6.59 (4.11-10.59)	2.47 (1.12-5.45)	-	1.24 (0.40-3.81)
Murashita	-	-	-	-
Nishioka	-	-	-	-
Pavie	4.45 (2.62-7.57)	-	-	0.17 (0.01-2.73)
Pavoni	6.49 (5.12-8.22)	2.03 (1.31-3.13)	0.51 (0.08-0.48)	-
Permanyer	-	-	-	-
Riess	3.68 (2.76-4.90)	0.74 (0.38-1.41)	0.16 (0.01-0.08)	0.98 (0.56-1.72)
Ruggieri	-	-	-	-
Said	-	-	-	-
Sidhu	4.17 (3.11-5.59)	1.55 (0.95-2.52)	1.16 (0.72-2.23)	-
Sjogren	13.21 (11.22-15.56)	7.19 (5.72-9.04)	2.43 (0.60-1.35)	0.05 (0.00-0.84)
Suttie	9.55 (8.47-10.76)	-	-	-
Vicchio	-	-	-	-
Walczak	-	-	-	-

95% confidence interval provided in parentheses. SUD: Sudden unexplained death.

Table S5. Individual study outcome estimates of late valve-related events after bioprosthetic AVR

First author	Re-intervention: valve-related (%/year)	SVD (%/year)	NSVD (%/year)	Endocarditis (%/year)	TE (%/year)	VT (%/year)	Bleeding (%/year)	Stroke (%/year)
Accola	0.12 (0.04-0.37)	-	-	-	-	-	-	0.04 (0.01-0.28)
Ali 2007	-	-	-	-	-	-	-	-
Ali 2006	-	-	-	0.32 (0.05-2.27)	-	-	-	-
Arinaga	0.43 (0.16-1.14)	0.21 (0.05-0.86)	0.43 (0.16-1.14)	0.21 (0.05-0.86)	0.64 (0.29-1.43)	-	0.32 (0.10-0.99)	0.64 (0.29-1.43)
Ashikhmina	-	-	-	-	-	-	-	-
Aymard	-	-	-	-	-	-	-	-
Bose	-	-	-	-	-	-	-	-
Chiappini	-	-	-	-	-	-	-	-
Colli	-	-	-	-	-	-	-	-
de Vincentiis	-	-	-	-	1.20 (0.60-2.39)	-	0.30 (0.08-1.20)	-
Doss	-	-	-	-	-	-	-	-
Dunning	-	-	-	-	-	-	-	-
Ennker	-	-	-	-	-	-	-	-
Filsoufi	-	-	-	-	-	-	-	-
Flameng	-	-	-	2.37 (0.34-16.46)	1.19 (0.08-18.66)	-	2.37 (0.34-16.46)	-
Florath	0.92 (0.48-1.77)	-	-	0.60 (0.27-1.34)	-	-	1.10 (0.61-1.99)	3.20 (2.27-4.52)
Folliguet	1.28 (0.32-5.08)	-	3.85 (1.75-8.43)	1.92 (0.63-5.90)	6.41 (3.52-11.68)	-	2.56 (0.97-6.75)	1.28 (0.32-5.08)
Gelsomino	-	-	-	-	1.80 (0.46-7.11)	-	0.45 (0.03-7.16)	0.90 (0.13-6.34)
Glaser	0.40 (0.21-0.74)	-	-	-	-	-	-	-
Hellgren	-	-	-	0.61 (0.43-0.87)	2.40 (2.01-2.86)	-	0.97 (0.73-1.28)	-
Kawachi	-	0.62 (0.04-9.76)	0.62 (0.04-9.76)	0.62 (0.04-9.76)	-	-	0.62 (0.04-9.76)	-
Kurlansky	0.05 (0.01-0.21)	-	-	-	-	-	-	-
Lehmann	-	-	-	0.24 (0.10-0.57)	-	0.05 (0.01-0.34)	-	0.43 (0.22-0.82)
Litmathe	-	-	-	-	-	-	-	-

Table S5. Continued

First author	Re-intervention: valve-related (%/year)	SVD (%/year)	NSVD (%/year)	Endocarditis (%/year)	TE (%/year)	VT (%/year)	Bleeding (%/year)	Stroke (%/year)
Luciani	0.85 (0.54-1.32)	0.71 (0.44-1.16)	-	-	-	-	-	-
Martinovic	0.31 (0.10-0.97)	-	-	-	1.14 (0.64-2.06)	-	0.05 (0.00-0.83)	0.31 (0.10-0.97)
Mistiaen	-	-	-	0.21 (0.01-3.29)	2.47 (1.12-5.45)	-	1.24 (0.40-3.81)	1.65 (0.62-4.36)
Murashita	-	-	-	-	-	-	-	-
Nishioka	-	0.10 (0.01-1.55)	-	0.58 (0.19-1.80)	-	-	-	0.78 (0.29-2.06)
Pavie	0.68 (0.17-2.73)	0.17 (0.01-2.73)	0.34 (0.05-2.42)	0.68 (0.17-2.73)	0.17 (0.01-2.73)	-	0.34 (0.05-2.42)	-
Pavoni	2.94 (2.05-4.21)	3.34 (2.39-4.68)	1.11 (0.62-2.01)	0.71 (0.34-1.48)	-	-	-	-
Permanyer	-	-	-	-	-	-	-	-
Riess	0.74 (0.38-1.41)	0.16 (0.04-0.65)	0.16 (0.04-0.65)	0.16 (0.04-0.65)	1.06 (0.62-1.83)	0.25 (0.08-0.76)	0.33 (0.12-0.87)	0.25 (0.08-0.76)
Ruggieri	-	0.25 (0.16-0.37)	-	-	-	-	-	-
Said	0.70 (0.58-0.84)	-	-	-	-	-	-	-
Sidhu	-	0.10 (0.01-0.69)	0.10 (0.01-0.69)	0.58 (0.26-1.29)	1.84 (1.18-2.88)	0.05 (0.00-0.78)	-	-
Sjogren	-	1.16 (0.65-2.09)	0.05 (0.00-0.84)	0.74 (0.35-1.55)	3.59 (2.58-5.00)	-	0.63 (0.29-1.41)	2.75 (1.88-4.01)
Suttie	0.39 (0.21-0.73)	-	-	-	-	-	-	-
Vicchio	-	-	-	-	-	-	-	-
Walczak	-	-	-	-	-	-	-	-

95% confidence interval provided in parentheses. SVD: Structural valve deterioration. NSVD: Non-structural dysfunction. TE: Thromboembolism. VT: Valve thrombosis.

Table S6. Least squares regression of modeled survival vs. observed survival for estimation of excess mortality not directly related to valve-related events

Hazard ratio[1]	Sum of squared residuals[2]
0.80	3476.2
0.85	2918.4
0.86	**2888.9**
0.87	2891.8
0.90	3044.0
1.00	4976.8

Bold print indicates the selected model. [1]Hazard ratio of background mortality + excess mortality relative to background mortality. [2]Sum of squared residuals between microsimulation-based survival and survival observed in our meta-analysis of Kaplan-Meier freedom from all-cause mortality.

Table S7. Microsimulation results of the reasons of interventions and causes of death after AVR

Age at surgery	75 years	85 years
Reason for re-intervention		
Structural valve deterioration	36%	27%
Non-structural valve dysfunction	20%	24%
Endocarditis	32%	37%
Valve thrombosis	13%	12%
Cause of death		
Early mortality	5%	5%
Structural valve deterioration	1%	0%
Non-structural valve dysfunction	0%	0%
Endocarditis	2%	1%
Thromboembolism	6%	4%
Valve thrombosis	0%	0%
Bleeding	3%	2%
Re-intervention	1%	1%
Background and excess mortality	81%	87%

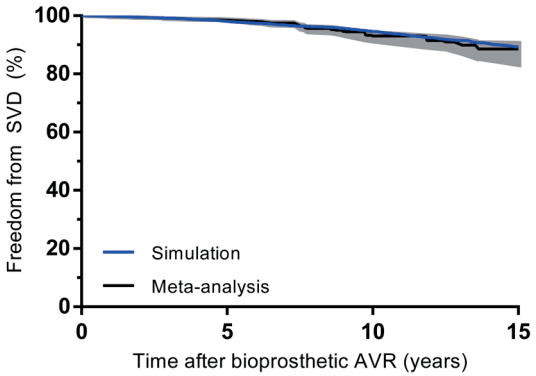
Table S8. Univariable random effects meta-regression results of bioprostheses studies

	Early mortality		Early renal failure		Late SVD	
	β (95%CI)	p-value	β (95%CI)	p-value	β (95%CI)	p-value
Study design (prospective vs. retrospective)	-0.25 (-0.72-0.22)	0.301	0.02 (-1.33-1.37)	0.974	-1.06 (-2.81-0.69)	0.235
Median year of valve replacement	-0.02 (-0.05-0.01)	0.113	-0.03 (-0.08-0.03)	0.392	0.02 (-0.12-0.16)	0.751
Mean follow-up duration (/year increase)					-0.04 (-0.30-0.21)	0.737
Mean age (/year increase)	**0.08 (0.03-0.13)**	**0.001**	0.05 (-0.03-0.13)	0.262	-0.02 (-0.34-0.29)	0.878
Male	-0.30 (-2.31-1.70)	0.766	1.87 (-1.66-5.40)	0.299	-1.96 (-16.04-12.11)	0.785
Emergency surgery	1.22 (-0.24-2.69)	0.102	0.63 (-2.18-3.43)	0.662		
NYHA class I/II	0.14 (-1.86-2.15)	0.888	-2.93 (-8.83-2.97)	0.330	2.84 (-16.13-21.80)	0.769
NYHA class III/IV	-0.42 (-2.21-1.37)	0.647	0.81 (-3.87-5.48)	0.736	-2.84 (-21.80-16.13)	0.769
AS	0.94 (-0.19-2.07)	0.102	0.90 (-0.31-2.11)	0.144	0.33 (-3.99-4.65)	0.881
AI	-0.12 (-2.87-2.62)	0.929	2.98 (-3.72-9.69)	0.384	-2.74 (-12.34-6.86)	0.576
AS/AI	-1.01 (-2.24-0.22)	0.109	-0.17 (-1.64-1.30)	0.822	0.21 (-3.88-4.30)	0.919
Concomitant CABG	-0.13 (-1.49-1.22)	0.845	2.36 (-5.49-10.21)	0.556	1.74 (-7.65-11.13)	0.716
Type of valve (porcine vs. pericardial)	**0.54 (0.11-0.96)**	**0.013**	0.30 (-1.07-1.68)	0.665	0.24 (-1.89-2.37)	0.824
	Late NSVD		**Late TE**		**Late bleeding**	
	β (95%CI)	p-value	β (95%CI)	p-value	β (95%CI)	p-value
Study design (prospective vs. retrospective)	0.99 (-1.25-3.23)	0.388	0.11 (-0.70-0.92)	0.791	-0.07 (-1.09-0.96)	0.899
Median year of valve replacement	**0.17 (0.08-0.26)**	**0.000**	0.01 (-0.05-0.07)	0.719	0.05 (-0.03-0.13)	0.188
Mean follow-up duration (/year increase)	**-0.39 (-0.77--0.01)**	**0.044**	-0.10 (-0.30-0.10)	0.312	**-0.21 (-0.39--0.03)**	**0.025**
Mean age (/year increase)	0.05 (-0.25-0.35)	0.742	0.10 (-0.02-0.21)	0.105	0.09 (-0.07-0.25)	0.262
Male	**-11.82 (-21.04--2.60)**	**0.012**	-5.40 (-11.15-0.35)	0.066	-5.48 (-13.41-2.44)	0.175
Emergency surgery	-7.47 (-63.37-48.43)	0.793	-7.45 (-30.27-15.37)	0.522	-5.23 (-21.56-11.11)	0.530
NYHA class I/II	-7.11 (-17.87-3.64)	0.195	-4.01 (-9.83-1.82)	0.178	-2.23 (-7.06-2.61)	0.367
NYHA class III/IV	7.11 (-3.64-17.87)	0.195	4.01 (-1.82-9.83)	0.178	2.23 (-2.61-7.06)	0.367
AS	-0.47 (-4.17-3.22)	0.802	0.72 (-1.40-2.84)	0.507	1.37 (-0.27-3.02)	0.101
AI	-2.08 (-10.20-6.05)	0.617	**-5.96 (-9.98--1.95)**	**0.004**	-4.27 (-9.74-1.21)	0.127
AS/AI	0.05 (-3.84-3.94)	0.980	-0.02 (-3.00-2.95)	0.987	-0.77 (-2.63-1.10)	0.420
Concomitant CABG	-7.29 (-16.85-2.28)	0.135	-0.01 (-1.92-1.91)	0.994	0.78 (-0.68-2.23)	0.295
Type of valve (porcine vs. pericardial)	-0.44 (-2.75-1.87)	0.711	-0.86 (-1.88-0.15)	0.096	-0.74 (-1.88-0.41)	0.206

Table S8. Continued

	Late stroke		Re-intervention		Late mortality	
	β (95%CI)	**p-value**	**β (95%CI)**	**p-value**	**β (95%CI)**	**p-value**
Study design (prospective vs. retrospective)	-1.00 (-2.09-0.09)	0.071	-0.64 (-2.08-0.80)	0.386	-0.36 (-0.79-0.07)	0.100
Median year of valve replacement	-0.03 (-0.16-0.09)	0.623	0.10 (-0.01-0.22)	0.088	-0.01 (-0.05-0.02)	0.432
Mean follow-up duration (/year increase)	-0.21 (-0.60-0.18)	0.283	-0.35 (-0.87-0.18)	0.194	0.06 (-0.04-0.17)	0.243
Mean age (/year increase)	0.24 (-0.01-0.49)	0.056	-0.03 (-0.22-0.16)	0.746	**0.08 (0.02-0.13)**	**0.007**
Male	-7.97 (-16.39-0.45)	0.064	-1.77 (-8.33-4.78)	0.596	1.83 (-0.01-3.67)	0.051
Emergency surgery	11.31 (-17.87-40.49)	0.447	0.33 (-19.51-20.17)	0.974	-2.28 (-8.63-4.07)	0.482
NYHA class I/II	-0.43 (-8.32-7.45)	0.914	0.69 (-2.89-4.27)	0.706	-2.46 (-5.42-0.49)	0.102
NYHA class III/IV	0.43 (-7.45-8.32)	0.914	-0.68 (-4.26-2.89)	0.708	2.46 (-0.50-5.42)	0.103
AS	3.88 (1.19-6.57)	0.005	1.49 (-2.51-5.49)	0.466	**1.05 (0.02-2.08)**	**0.045**
AI	-2.92 (-9.39-3.55)	0.376	-1.28 (-10.37-7.82)	0.783	**-3.01 (-5.19--0.83)**	**0.007**
AS/AI	-2.65 (-6.53-1.23)	0.181	-2.01 (-6.80-2.77)	0.409	-0.61 (-1.77-0.54)	0.297
Concomitant CABG	-1.56 (-8.05-4.94)	0.639	0.14 (-1.55-1.82)	0.875	0.52 (-0.24-1.28)	0.180
Type of valve (porcine vs. pericardial)	-0.25 (-1.80-1.29)	0.747	0.02 (-1.33-1.37)	0.977	**-0.60 (-1.07--0.13)**	**0.012**

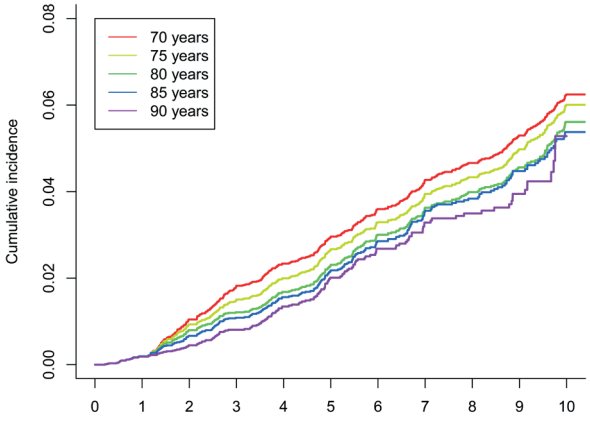
SVD: structural valve deterioration. NSVD: non-structural valve dysfunction. TE: thromboembolism. SUD: sudden unexpected death. NYHA: New York Heart Association. AS: aortic stenosis. AI: aortic insufficiency. CABG: coronary artery bypass grafting.



Number of patients at risk			
1509	875	387	93
10000	7478	4640	2203

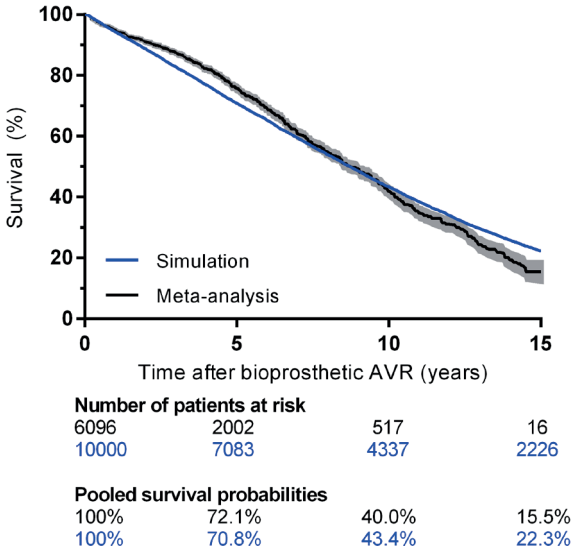
Pooled freedom from S VD			
100%	98.7%	93.0%	88.5%
100%	98.1%	94.6%	89.3%

Figure S1. Gompertz distribution (shape 0.124, rate 0.003) fitted to pooled Kaplan-Meier curve of freedom from SVD after bioprosthetic aortic valve replacement (AVR). SVD: structural valve deterioration.



Cumulative incidence		
70 years	0.030	0.062
75 years	0.027	0.060
80 years	0.023	0.056
85 years	0.022	0.054
90 years	0.020	NA

Figure S2. Cumulative incidence functions of structural valve deterioration and mortality for different age groups.



Number of patients at risk

6096	2002	517	16
10000	7083	4337	2226

Pooled survival probabilities

100%	72.1%	40.0%	15.5%
100%	70.8%	43.4%	22.3%

Figure S3. Calibration plots of the microsimulation model.

Microsimulation-based actuarial survival is plotted against observed pooled Kaplan-Meier survival curves (age- and gender-matched).

6

Beyond the clinical impact of aortic and pulmonary valve implantation

Health-related quality of life, informal care, and productivity

Simone A. Huygens, Frank van der Kley, Jos A. Bekkers, Ad J.J.C. Bogers,
Johanna J.M. Takkenberg, Maureen P.M.H. Rutten-van Mölken.

EJCTS. In press.

ABSTRACT

Objective: Our aim was to provide estimates of patient-reported health-related quality of life, use of informal care and productivity in patients after surgical aortic and pulmonary valve replacement and transcatheter aortic valve implantation (TAVI).

Methods: Consecutive cohorts of 1,239 adult patients who had surgical aortic valve replacement or surgical pulmonary valve replacement and 433 patients who had TAVI at 2 Dutch heart centres were cross-sectionally surveyed at a median time of 2.9 and 3.2 years after the intervention, respectively. The survey included questions on health-related quality of life (EQ-5D-5L and SF-12-v2), use of informal care and productivity in paid and unpaid work. All outcomes were compared with age and sex-matched individuals from the general population.

Results: The response rate was 56% (n=687) of patients who had surgical valve replacement and 59% (n=257) of those who had TAVI. Compared with the general population, patients reported poorer health-related quality of life on physical health domains, whereas their scores were comparable for mental health domains. After a heart valve implantation, patients reported using informal care more frequently than the general population, but labour participation was comparable. Patients with late complications (antibiotic treatment for endocarditis [n=4], stroke [n=11], transient ischaemic attack [n=15]) reported lower health-related quality of life, greater use of informal care and greater productivity loss than patients without complications.

Conclusion: Patients who had aortic and pulmonary valve implantations experience relatively mild limitations in daily life compared to the general population. The consequences of a heart valve implantations beyond clinical outcomes should be considered to create realistic patient expectations of life after a heart valve implantation and unbiased resource allocation decisions at national levels.

INTRODUCTION

Increasing attention is paid to optimal tailoring of heart valve interventions to individual patients. In making those choices, many factors should be considered, including morbidity, mortality, quality of life, patient needs, preferences and capabilities.[1] In addition to the consequences for patients, a heart valve implantation can also impact others: Family or friends may have to provide informal care to patients, and society is influenced by changes in the productivity of patients.

Empirical evidence of these outcomes is necessary to be able to consider them in treatment decisions of individual patients and in allocation of limited health care resources to interventions that yield the most value for money. Traditionally, research on outcomes after a heart valve implantation focuses on mortality, morbidity and re-intervention.[2-4] In addition to clinical outcomes, health-related quality of life (HRQoL) has received more attention in the last decade. Several studies showed that HRQoL in patients with heart valve disease who receive no or conservative treatment is impaired and deteriorates over time [5-7], whereas surgical and transcatheter valve implantation result in improvements in HRQoL to levels close to or even better than those in the general population.[5,8-12] However, to our knowledge, there are no studies on informal care and productivity after a heart valve implantation.[13] These aspects are not only important to patients and their families and friends but also to society in general. The costs of informal care (21-30%) and productivity loss (17-29%) comprise a considerable proportion of the societal costs of patients with cardiovascular diseases.[14,15] Several countries, including the Netherlands, emphasize the importance of these outcomes in decision making by making it obligatory to perform a cost-effectiveness study from a societal perspective including productivity loss and informal care costs before considering reimbursement from health care insurance.[16]

This study was performed to inform early health technology assessment (HTA) of tissue-engineered heart valves (TEHV) in which the potential cost-effectiveness of these valves in the pulmonary and aortic positions was assessed.[17] We focused on the pulmonary position because tissue-engineered heart valves are expected to have large benefits in patients with congenital heart disease, often involving the pulmonary valve. In addition, we focused on the aortic position because patients with aortic valve disease represent the largest target population for tissue-engineered heart valves. The aim of this study was to provide an overview of the impact of heart valve implantations beyond clinical outcomes by reporting the results obtained from responses to patient-reported questionnaires on HRQoL, informal care and productivity from patients who had aortic and pulmonary valve implantation. The results are placed in perspective by comparing them to age and sex-matched individuals from the general population.

METHODS

Patient population

This study was approved by the institutional review board (Erasmus MC MEC-2015-483) and informed consent was obtained from all participants. Between 1 January 2010 and 31 December 2016, 1266 consecutive patients underwent surgical aortic valve replacement (SAVR) or surgical pulmonary valve replacement (SPVR) in the Erasmus Medical Center, the Netherlands, and between 1 January 2010 and 1 December 2017, 490 consecutive patients underwent transcatheter aortic valve implantation (TAVI) in the Leiden University Medical University Center, Rotterdam,, the Netherlands. Patients with an available postal address who were alive according to the civil registry, ≥18 years old and not participating in another study at the time the questionnaires were sent (surgical valve replacement [SVR]: n=1239, 98%; TAVI: n=433, 88%) were requested to complete and return a postal questionnaire. If there was no response within 6 weeks, patients were reminded by letter.

Patient perioperative clinical and intervention characteristics and events during the follow-up period (Supplementary Material) were collected from hospital records. To be able to estimate the outcomes specifically for patients who experienced late complications after having a heart valve implantation, patients who had SAVR and SPVR were divided in groups with and without late complications during follow-up (>30 days postintervention) based on data extracted from hospital records (including records from referring hospitals). Complications included stroke, transient ischaemic attack (TIA), bleeding and conservative treatment (i.e. no re-intervention) for prosthetic valve dysfunction, valve thrombosis and endocarditis. Patients without late complications were asked about the last 4 weeks, whereas patients who experienced late complications were asked to recall the first 4 weeks after the complication. This distinction was not made for patients who had TAVI because we did not have access to their hospital records beyond the postintervention in-hospital period. Instead they were all asked about the last 4 weeks after the procedure.

Questionnaire

The questionnaire started with questions about marital status, education and income level. HRQoL was measured with the *EQ-5D-5L* and *SF-12-v2*.[18,19] Health states derived from these questionnaires were assigned a utility (ranging from 0 to 1, with 1 representing full health) using scoring algorithms.[20,21]

The *Valuation of Informal Care Questionnaire* was completed by the main informal caregiver and included questions on type and amount of informal care.[22] Informal care was divided into household activities (e.g. preparing drinks/food and cleaning),

personal care (e.g. help with getting dressed and toilet visits) and practical support (e.g. financial and administrative tasks).
The *Productivity Cost Questionnaire* included questions about paid and unpaid work.[23] Unpaid work included volunteer work, babysitting, grocery shopping and so forth. Productivity during paid work was expressed in absenteeism (not attending work) and presenteeism (diminished quantitative or qualitative functioning while attending work).[24]

Statistical analyses
Statistical analyses were performed in R (Version 3.3.2). For every treatment cohort, we performed descriptive analyses of patient and intervention characteristics, complications, HRQoL, informal care use and productivity loss. Continuous variables were depicted as means and standard deviations or medians and interquartile ranges and discrete variables as counts and proportions. The results were compared with estimates from the age and/or sex matched general population (Supplementary Material). The associations between HRQoL (EQ-5D-5L utility) and informal care or productivity were tested with Mann-Whitney tests (difference between groups) and the Spearman correlation (2 continuous variables). The influence of patient and intervention characteristics on EQ-5D utilities was estimated with regression analyses(Supplementary Material).

RESULTS

In total, 687 patients who had SVR (56%) and 257 who had TAVI (59%) returned the questionnaire. Patient and intervention characteristics are presented in Table 1; postoperative complications and age and sex of responders and non-responders are provided in Table S1 and S2. Thirty patients who had SVR were asked to recall what happened during the 4 weeks after they experienced a specific complication (Table S3): hospitalization for endocarditis (n=4), stroke (n=11) or TIA (n=15). The median time between the complication and completing the questionnaire was 2.1 years. Other patients who had SVR were asked about the last 4 weeks and were divided into patients who had SAVR (n=633) and those who had SPVR (n=26). Two patients underwent both SAVR and SPVR and were included in both groups. The median time since intervention was 2.9 years for patients who had SAVR, 3.2 years for those who had SPVR and 1.1 years for those who had TAVI. Unless stated otherwise, reported results concern patients without late complications. Results of patients with complications can be found in the Supplemental Material.

Health-related quality of life

EQ-5D-5L

Compared with the general population, patients who had SAVR and TAVI had lower utilities; patients with SPVR had higher utilities (Figure 1, Table 1, Table S4-5). Of the patients with late complications, patients admitted to the hospital for endocarditis had the lowest EQ-5D-5L utility during the 4 weeks after the complication (n=4, 0.294 ± 0.452), followed by stroke (n=11, 0.629±0.304) and TIA (n=13, 0.879 ± 0.223; Table S6). Results of regression analyses of EQ-5D utilities are provided in Table S7-8.

SF-12-v2 and SF-6D

Compared to the general population (mean ± standard deviation [SD]: 50±10), patients scored lower on most SF-12 dimensions and on the physical component score (Figure 2, Table S9). The physical component and the mental component scores after complications were also lower than those from the general population: 42.5 and 47.7, respectively (Table S10).

The means and SDs of SF-6D utilities were 0.742±0.131 (n=543) in patients having SAVR, 0.759±0.115 (n=26) in those having SPVR, and 0.667±0.109 (n=200) in those having TAVI (Table S11). The mean SF-6D utility after complications was 0.696±0.122 (n=26; Table S12-13).

Informal care

During the last 4 weeks, 16% of patients who had SAVR, 15% of those who had SPVR and 35% of those who had TAVI received informal care (Table 2). These values are higher than those for the general population (12%, 5% and 21% for the general population comparable to those for patients who had SAVR, SPVR or TAVI, respectively). Only patients >75 years who had SAVR used less informal care than the general population (16% vs. 25%). The amount of informal care was lower than that in the general population (SAVR 16.1 vs. 20.4 hours/week; SPVR, 10.0 vs. 23.1 hours/week; TAVI 10.5 vs. 18.8 hours/week).

After a complication, 26.7% of patients used informal care. The amount of informal care was high (on average 43.1 hours/week), especially due to personal care. Patients who experienced strokes used informal care most often (45.5%), followed by endocarditis (25.0%) and TIA (13.3%; Table S14).

Table 1. Patient characteristics and health-related quality of life at the time of the questionnaire and intervention characteristics

	SAVR	SPVR	TAVI
Number	633	26	257
Age, median (IQR)	69.6 (61.2-76.6)	35.8 (26.2-45.5)	83.3 (53.1-87.4)
Age, range	18.4-91.2	18.7-69.6	53.1-98.1
Age group, n (%)			
19-60 years	141 (22.3)	22 (84.6)	2 (0.8)
61-70 years	195 (30.8)	4 (15.4)	13 (5.1)
>70 years	297 (46.9)	0(0)	242 (94.2)
Male, n (%)	438 (69.2)	16 (61.5)	155 (60.3)
Partner, n (%)	435 (73.7)	11 (45.8)	132 (56.7)
Income above median, n (%)*	212 (33.5)	7 (26.9)	71 (27.6)
High education level, n (%)†	278 (43.9)	16 (61.5)	85 (33.1)
Years since intervention, median (IQR)	2.9 (1.4-4.5)	3.2 (1.7-4.8)	1.1 (0.3-2.5)
Approach, n (%)			
Surgical	633 (100)	26 (100)	-
Transapical	-	-	46 (17.9)
Transfemoral	-	-	211 (82.1)
Multiple valve replacement, n (%)	62 (9.8)	5 (19.2)	-
Concomitant CABG, n (%)	167 (26.4)	0(0)	-
Valve type, n (%)			
Biological	377 (59.4)	22 (84.6)	-
Mechanical	248 (39.2)	3 (11.5)	-
Unknown	8 (1.3)	1 (3.8)	-
Previous valve replacement, n (%)	50 (7.9)	8 (30.8)	-
Logistic EuroSCORE, median (IQR)	5.6 (3.5-9.6)	4.0 (4.0-5.5)	12.5 (8.6-20.8)
Health-related quality of life			
Visual analogue scale (VAS), mean ± SD (n)	75.4 ± 16.8 (616)	82.3 ± 14.1 (26)	67.3 ± 16.7 (229)
EQ-5D patients, mean ± SD (n)	0.844 ± 0.196 (618)	0.934 ± 0.115 (26)	0.711 ± 0.249 (241)
EQ-5D general population, mean ± SD	0.869 ± 0.077	0.884 ± 0.107	0.845 ± 0.176

*Net household income > €2.500. † >4 years high school or higher education.
SAVR: surgical aortic valve replacement. SPVR: surgical pulmonary valve replacement. TAVI: transcatheter aortic valve implantation. IQR: interquartile range. SD: standard deviation. CABG: coronary artery bypass grafting.

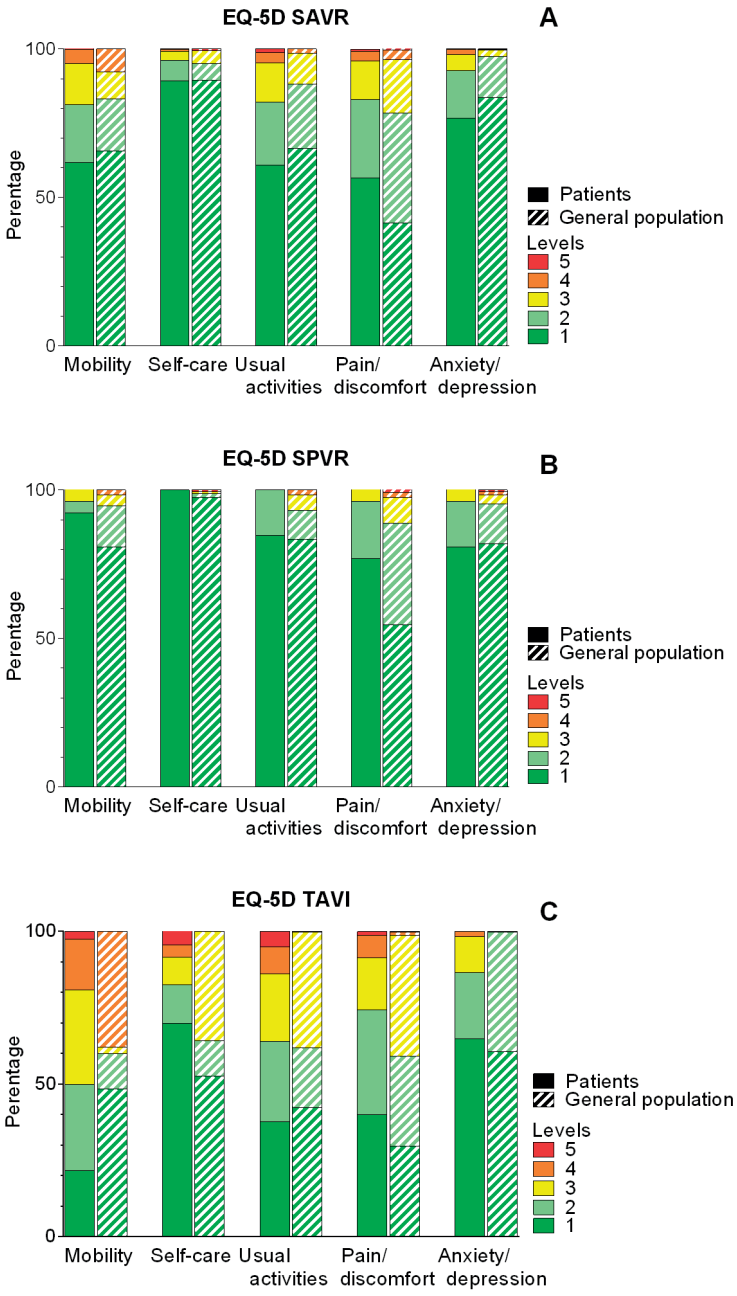


Figure 1. EQ-5D-5L domain scores per treatment compared with the general population. EQ-5D: Higher level indicates poorer health-related quality of life. SAVR: surgical aortic valve replacement; SPVR: surgical pulmonary valve replacement; TAVI: transcatheter aortic valve implantation

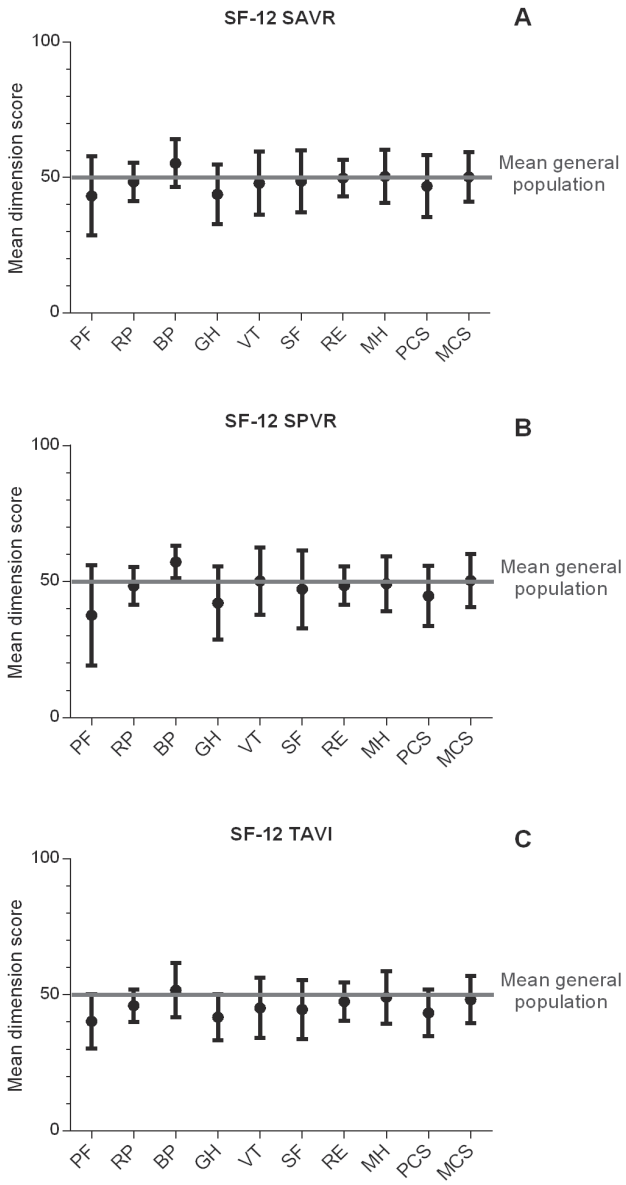


Figure 2. SF-12-v2 dimension and summary component scores compared with the general population. SF-12: Higher score indicates better health-related quality of life. Horizontal line represents mean value for general population. SAVR: surgical aortic valve replacement. SPVR: surgical pulmonary valve replacement. TAVI: transcatheter aortic valve implantation. PF: physical functioning. RP: role physical. BP: bodily pain. GH: general health. VT: vitality. SF: social functioning. RE: role emotional. MH: mental health. PCS: physical component score. MCS: mental component score.

Productivity

Most patients who worked before the intervention (SAVR, 34.9%; SPVR, 73.1%) were able to resume paid work afterwards (SAVR, 74.2%; SPVR 89.5% of employed patients; Table 3). The majority of patients who had TAVI were unemployed before the intervention (97%). The 6 employed patients resumed working after TAVI.

The proportions of patients <75 years old who had SAVR and who had SPVR who worked were comparable to the general population (SAVR 43.6% vs. general population 43.3%; SPVR 73.1% vs. general population 72.9%).

The proportion of patients with absenteeism was lower than that in the general population in patients who had SAVR (18.2% vs. 38.7%) and those who had SPVR (1.7% vs. 45.3%), but the proportion of days absent out of total work days was higher in patients who had SAVR (10.4% vs. 4.2%) and lower in those who had SPVR (1.1% vs. 3.1%) than in the general population.

After complications patients were often absent from paid and unpaid work for a longer period (20.0 days; Table S15).

Table 2. Informal care during the past 4 weeks

	SAVR (n=633)		SPVR (n=26)		TAVI (n=257)	
		Hours per week		Hours per week		Hours per week
All patients						
Informal care received	103 (16.3)	21.0±31.2	4 (15.4)	12.5±11.7	90 (35.0)	20.5±20.7
Type of informal care						
Household activities	76 (12.0)	12.1±13.4	3 (11.5)	12.0±13.3	70 (27.2)	12.0±13.1
Personal care	42 (6.6)	11.3±14.3	0 (0.0)	0.0±0.0	40 (15.6)	8.9±14.4
Practical support	82 (13.0)	9.1±12.4	4 (15.4)	2.5±0.6	76 (29.6)	8.4±8.8
Total duration of informal care, years	4.6±6.9		9.3±17.1		6.4±6.4	
Costs per week, €*						
All patients	47±208		28±88		101±222	
Patients who received informal care	301±447		179±168		293±296	
Informal care recipients characteristics	n=103		n=4		n=90	
Age, years	67.9±12.5		44.3±17.6		82.4±7.4	
Sex, n						
Male	58 (56.3)		2 (50.0)		46 (51.1)	
Female	45 (43.7)		2 (50.0)		44 (48.9)	
Informal caregiver characteristics	n=103		n=4		n=90	
Age, years	60.7±13.6		61.8±8.4		66.1±12.4	
Sex, n						
Male	36 (35.0)		1 (25.0)		23 (25.6)	
Female	64 (62.1)		3 (75.0)		63 (70.0)	
Missing	3 (2.9)		0 (0.0)		4 (4.4)	
Relationship with patient, n						
Partner	69 (67.0)		1 (25.0)		41 (45.6)	
Child	17 (16.5)		2 (50.0)		31 (34.4)	
Parent (including in-law)	4 (3.9)		1 (25.0)		6 (6.7)	
Other relative	4 (3.9)		0 (0.0)		1 (1.1)	
Friend	2 (1.9)		0 (0.0)		6 (6.7)	
Other	5 (4.9)		0 (0.0)		2 (2.2)	
Missing	2 (1.9)		0 (0.0)		3 (3.3)	

Results presented as mean±standard deviation or n (%). *Societal cost of informal care was calculated by multiplying the amount of informal care with the replacement costs of household care (€14.32 per hour in 2017).[16] SAVR: surgical aortic valve replacement. SPVR: surgical pulmonary valve replacement. TAVI: transcatheter aortic valve implantation. SD: standard deviation.

Table 3. Productivity

	SAVR (n=633)	SPVR (n=26)	TAVI (n=257)
Paid work after intervention			
Change in employment after intervention			
No paid work before or after intervention	395 (62.4)	4 (15.4)	250 (97.3)
Quit	57 (9.0)	2 (7.7)	1 (0.4)
Less	31 (4.9)	0 (0.0)	1 (0.4)
Same	123 (19.4)	16 (61.5)	5 (1.9)
More	10 (1.6)	1 (3.8)	0 (0.0)
Started working after intervention	17 (2.7)	3 (11.5)	0 (0.0)
Sick leave after intervention, weeks	16.5±12.8	13.1±8.8	5.1±5.6
Productivity costs in employed patients*, €	16,281±8,607	13,342±7,280	7,250±8,137
Productivity costs in all patients, €	5,231±9,034	11,022±8,373	142±1434
Paid work last 4 weeks	n=181	n=20	n= 6
Absenteeism			
Yes	33 (18.2)	3 (15.0)	0 (0.0)
No	114 (63.0)	16 (80.0)	4 (66.7)
Missing	34 (18.8)	1 (5.0)	2 (33.3)
Days during the past 4 weeks	10.9±9.6	8.5±7.8	-
Proportion of days absenteeism (all patients)	10.4±0.3	1.1±4.5	0.0±0.0
Productivity costs in employed patients, €	10,167±12,159	877±-	-
Productivity costs in all patients, €	2,062±6,781	52±213	-
Presenteeism			
Yes	28 (15.5)	4 (20.0)	1 (16.7)
No	106 (58.6)	14 (70.0)	2 (33.3)
Missing	47 (26.0)	2 (10.0)	3 (50.0)
Days during the past 4 weeks	9.5±7.9	6.8±7.1	4±-
Productivity†	6.3±2.5	7.3±1.3	8±-
Unpaid work last 4 weeks	n=633	n=26	n=257
Yes	259 (40.9)	13 (50.0)	67 (26.1)
No	319 (50.4)	13 (50.0)	153 (59.5)
Missing	55 (8.7)	0 (0.0)	37 (14.4)
Productivity of patients with unpaid work			
Less unpaid work	62 (23.9)	1 (7.7)	21 (31.3)
Days during the past 4 weeks	12.1±8.2	10.0±1.0	14.0±9.6
Hours/day during the past 4 weeks	3.8±3.7	4.0±1.0	4.1±4.5
Productivity costs in patients with unpaid work‡, €	625±716	573±-	657±808
Productivity costs in all patients‡, €	60±290	23±115	60±304

Results presented as mean±standard deviation or n (%).
*Productivity cost of paid work was determined using the friction cost method and the average labor costs per hour for men and women (€40.31 and €33.61 per hour, respectively).[16]
†Scale from 0 to 10: 10 is not limited at all during work-related activities.
‡Productivity costs of lost hours of unpaid work were calculated by multiplying the number of lost hours of unpaid work with the replacement costs of household care (€14.32 per hour in 2017).[16]
SAVR: surgical aortic valve replacement; SPVR: surgical pulmonary valve replacement; TAVI: transcatheter aortic valve implantation; €: euros

Associations between health-related quality of life and use of informal care or productivity

HRQoL was significantly lower in patients receiving informal care compared to patients without informal care (SAVR: 0.697 vs. 0.872, p<0.000; TAVI: 0.613 vs. 0.762, p<0.000). Correlations between numbers of hours of informal care and HRQoL were weak (SAVR: -0.18; TAVI: -0.23).

HRQoL was significantly lower in patients who had SAVR who reported absenteeism or presenteeism compared to patients without productivity loss (absenteeism: 0.817 vs. 0.930, p<0.000; presenteeism: 0.776 vs. 0.945). Correlations between numbers of days of absenteeism or presenteeism and HRQoL were weak (absenteeism: -0.37; presenteeism: -0.38).

Patients who had SAVR who performed unpaid work reported slightly higher HRQoL than patients without unpaid work (0.867 vs. 0.836, p=0.123). The difference in HRQoL was larger in patients who had TAVI with or without unpaid work (0.793 vs. 0.690, p=0.017). The number of days patients could perform less unpaid work was moderately associated with HRQoL (SAVR: -0.47; TAVI: -0.52).
These analyses were not performed for SPVR because of the small number of patients included in this cohort.

DISCUSSION

Our results indicate that patients who have aortic or pulmonary valve implantations in the Dutch health care setting experience relatively mild limitations in daily life compared to the general population. Patients had impaired HRQoL, mostly reflected in poorer physical health, whereas mental health was comparable to that of the general population. Patients more often used informal care than the general population, but the amount of informal care was lower than that in other persons receiving informal care in the general population. Finally, labor participation was comparable and patients were less often absent from work; however, when patients called in sick they were absent longer than people in the general population. These results should be communicated to patients to create realistic expectations about their life after a heart valve implant.

In addition, societal outcomes (i.e. informal care and productivity loss) should be considered in resource allocation decisions. Otherwise, cost-effectiveness calculations will be biased and hence may result in wrong policy information and decisions.[25,26] For example, imagine a new expensive heart valve implantation that results in small improvements in clinical outcomes, but due to the invasiveness of the procedure, patients use more informal care

afterwards. When the increased use of informal care is not taken into account, the additional health benefits may be large enough to offset the increased costs of the procedure. However, the increase in informal care is associated with costs for society.[16] If these costs are taken into account, the health benefits may be too small to offset the increased costs of the procedure and informal care. Instead the limited health care budget should be spent on health care interventions that can yield more value for the money.[1]

Health-related quality of life

Although the HRQoL of the patients who had SAVR and TAVI was lower than that in the general population, the impairment was relatively mild. In fact, patients who had SPVR even had a slightly better HRQoL than the general population.

In accordance with results from previous studies, patients after heart valve implants had impaired physical HRQoL, whereas mental HRQoL was comparable or slightly better than in the general population.[8-10,27] This result may be caused by patients adapting to their health state by learning new coping skills or changes in lifestyle and activities.[27,28] Furthermore, a life-threatening experience (e.g. cardiac surgery) may result in changes in internal standards and values. In other words, they may worry less about futilities in life.[27] In line with previous studies, patients across all treatment cohorts reported less bodily pain and discomfort than the general population.[8-10] This finding may be explained by symptom relief and return to their previous lifestyle after the heart valve implantation that changed the perception of their health status.[9]

The relatively poor HRQoL of patients who had TAVI compared to people in the general population is probably caused by selection of frail elderly to undergo TAVI, because it is a less invasive treatment than cardiac surgery.

The EQ-5D is the most commonly used instrument to calculate utilities and in turn quality-adjusted life years.[29] However, in clinical studies, the SF-36 and SF-12 are often used to measure HRQoL. There are algorithms available to convert SF-36 or SF-12 results into utilities (SF-6D).[21] In line with previous studies, we found that results of both instruments are not interchangeable; SF-6D utilities are considerably lower than EQ-5D utilities (both based on value sets from the United Kingdom, because a Dutch SF-12 value set was unavailable); SAVR: 0.742 vs. 0.875; SPVR: 0.759 vs. 0.951; TAVI: 0.667 vs. 0.754).[29,30] Furthermore, in line with previous research, we observed a ceiling effect in EQ-5D utility scores but not in SF-6D utility scores; 39% of patients who had SAVR, 65% of those who had SPVR and 12% of those who had TAVI reported full health on EQ-5D, whereas only 5%, 4%, and 0% of those who had SAVR, SPVR, and TAVI, respectively, reported full health on the SF-6D.[29] This finding stresses the importance of using the same utility instrument in all treatment groups when performing cost-effectiveness analyses. However, even when the same utility

instrument is used in all treatment groups, cost-effectiveness results can differ depending on which instrument is used. For example, small improvements in HRQoL in patients with mild conditions might result in larger utility differences (leading to better cost-effectiveness outcomes) using SF-6D compared to EQ-5D, because there is less room for improvement in EQ-5D utilities and SF-6D is more sensitive to smaller impairments.[29]

Informal care

Overall, patients who had a heart valve implant used informal care more often than the general population, but the amount of informal care was less. This suggests that, compared to other persons receiving informal care, the burden of caregiving is lower for patients after a heart valve implantation.

The use of informal care by the elderly undergoing SAVR was lower than that for the general population, whereas patients having TAVI more often used informal care than the general population. This finding probably reflects selection of relatively healthy elderly patients for SAVR and frail elderly patients for TAVI.

Productivity

Patients need considerable time (3-4 months) to recover after a surgical heart valve implantation before returning to work. Sick leave was shorter after TAVI (5 weeks). This difference might be due to the less invasive nature of TAVI; however there is probably a selection bias because the majority of patients had already retired before having TAVI (97%). Participation in the labour force by patients who had SAVR and SPVR was comparable with that of the general population. However, patients may have a lower occupation level, as was reported in patients with congenital heart disease.[27]

The proportion of patients who had SAVR and SPVR who were absent from work was substantially lower than in the general population; however, the proportion of days absent of the total working days in patients who had SAVR was higher than that in the general population. This result suggests that if patients who had SAVR were ill, they were more severely ill or needed more time to recover than the general population. However, absenteeism was only measured during the past 4 weeks, whereas yearly absenteeism was reported for the general population, increasing their probability of absenteeism.

Study limitations

Firstly, selection bias may have occurred, because 56-59% of patients responded and responders were older and more often men compared with nonresponders. The influence of this selection bias on outcomes is unclear. Healthier patients who were more capable of filling in the questionnaire may be over-represented, but it is also possible that less healthy patients are over-represented because healthier patients were too busy with work

or other activities to participate. Secondly, due to the small numbers of patients with late complications in the relatively short follow-up period and the considerable recall time, we could not report reliable estimates of HRQoL, informal care and productivity in patients after complications. Thirdly, the number of patients included in this study who had SPVR was small. However, the prevalence of pulmonary valve disease is much lower than that of aortic valve disease. Hence, the response in this small patient group was acceptable. Finally, SAVR and TAVI were not performed in the same centre.

Conclusion

This study is the first to report informal care use and productivity of patients after a heart valve implantation. Our results indicate that patients who have aortic and pulmonary valve implantations experience relatively mild limitations in daily life compared to the general population, reflected by impaired physical HRQoL, greater use of informal care, but comparable or even better mental HRQoL and labour participation. These consequences, in addition to the clinical outcomes, should be communicated to patients to create realistic expectations about their life after the heart valve implantation and should be included in cost-effectiveness analyses to ensure unbiased resource allocation decisions at national levels.

Acknowledgements. We would like to thank all participating referring hospitals for their cooperation and Bianca Ringelberg for her help with the distribution of questionnaires and data extraction from hospital records.

Funding. This work was supported by the Netherlands CardioVascular Research Initiative: The Dutch Heart Foundation, the Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences.

Conflicts of interest. None.

REFERENCES

1. Mokhles, M.M., S.A. Huygens, and M. Takkenberg, PhD, Johanna JM, *The risk in avoiding risk: Optimizing decision making in structural heart disease interventions.* Structural Heart, 2017: p. 1-7.
2. de Heer, F., et al., *Measuring what matters to the patient: health related quality of life after aortic valve and thoracic aortic surgery.* General thoracic and cardiovascular surgery, 2017: p. 1-7.
3. Korteland, N.M., et al., *Mechanical aortic valve replacement in non-elderly adults: meta-analysis and microsimulation.* European Heart Journal, 2017: p. ehx199.
4. Huygens, S.A., et al., *Contemporary outcomes after surgical aortic valve replacement with bioprostheses and allografts: a systematic review and meta-analysis.* European Journal of Cardio-Thoracic Surgery, 2016: p. ezw101.
5. Auensen, A., et al., *Patient-reported outcomes after referral for possible valve replacement in patients with severe aortic stenosis.* European Journal of Cardio-Thoracic Surgery, 2017. **53**(1): p. 129-135.
6. Van Geldorp, M.W.A., et al., *Quality of life among patients with severe aortic stenosis.* Netherlands Heart Journal, 2013. **21**(1): p. 21-27.
7. Reynolds, M.R., et al., *Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosisclinical perspective.* Circulation, 2011. **124**(18): p. 1964-1972.
8. Korteland, N.M., et al., *Quality of life and prosthetic aortic valve selection in non-elderly adult patients.* Interactive cardiovascular and thoracic surgery, 2016. **22**(6): p. 723-728.
9. Mokhles, M.M., et al., *Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit.* European Journal of Cardio-Thoracic Surgery, 2011. **40**(3): p. 571-578.
10. Chen, X.J., et al., *Bioprosthetic pulmonary valve replacement: Contemporary analysis of a large, single-center series of 170 cases.* J Thorac Cardiovasc Surg, 2013. **146**(6): p. 1461-1466.
11. Chatterjee, S., et al., *Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: an updated review of literature.* Current cardiology reports, 2014. **16**(4): p. 473.
12. Vicchio, M., et al., *Tissue Versus Mechanical Prostheses: Quality of Life in Octogenarians.* Ann Thorac Surg, 2008. **85**(4): p. 1290-1295.
13. Huygens, S.A., J.J.M. Takkenberg, and M.P.M.H. Rutten-van Mölken, *Systematic review of model-based economic evaluations of heart valve implantations.* The European Journal of Health Economics, 2017: p. 1-15.
14. Harnek, J., et al., *The 2011 outcome from the Swedish health care registry on heart disease (SWEDEHEART).* Scandinavian Cardiovascular Journal, 2013. **47**(sup62): p. 1-10.
15. Leal, J., et al., *Economic burden of cardiovascular diseases in the enlarged European Union.* European heart journal, 2006. **27**(13): p. 1610-1619.
16. Hakkaart-van Roijen, L., et al., *Kostenhandleiding.* Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. In opdracht van Zorginstituut Nederland. Geactualiseerde versie., 2015.

17. Huygens, S.A., et al., *Conceptual model for early health technology assessment of current and novel heart valve interventions.* Open Heart, 2016. **3**(2): p. e000500.
18. Ware, J.E., M. Kosinski, and D. Turner-Bowker, *User's Manual for the SF-12v2™ Health Survey with a Supplement Documenting SF-12® Health SurveyQualityMetric Incorporated*. 2001, Lincoln.
19. EuroQol, G., *EuroQol--a new facility for the measurement of health-related quality of life.* Health policy (Amsterdam, Netherlands), 1990. **16**(3): p. 199.
20. Versteegh, M.M., et al., *Dutch tariff for the five-level version of EQ-5D.* Value in health, 2016. **19**(4): p. 343-352.
21. Brazier, J.E. and J. Roberts, *The estimation of a preference-based measure of health from the SF-12.* Medical care, 2004. **42**(9): p. 851-859.
22. Hoefman, R., N. Exel van, and W. Brouwer, *iMTA Valuation of Informal Care Questionnaire.* 2013.
23. Bouwmans, C., et al., *The iMTA productivity cost questionnaire: a standardized instrument for measuring and valuing health-related productivity losses.* Value in Health, 2015. **18**(6): p. 753-758.
24. Krol, M., W. Brouwer, and F. Rutten, *Productivity costs in economic evaluations: past, present, future.* Pharmacoeconomics, 2013. **31**(7): p. 537-549.
25. Hoefman, R.J., J. van Exel, and W. Brouwer, *How to include informal care in economic evaluations.* Pharmacoeconomics, 2013. **31**(12): p. 1105-1119.
26. Krol, M., et al., *Do productivity costs matter?* Pharmacoeconomics, 2011. **29**(7): p. 601-619.
27. Opić, P., et al., *Psychosocial functioning of adults with congenital heart disease: outcomes of a 30–43 year longitudinal follow-up.* Clinical Research in Cardiology, 2015. **104**(5): p. 388-400.
28. Brazier, J., et al., *Should patients have a greater role in valuing health states?* Applied health economics and health policy, 2005. **4**(4): p. 201-208.
29. De Smedt, D., et al., *EQ-5D versus SF-12 in coronary patients: are they interchangeable?* Value in Health, 2014. **17**(1): p. 84-89.
30. Devlin, N., et al., *Valuing health-related quality of life: an EQ-5D-5L value set for England.* 2016

SUPPLEMENTAL MATERIAL

Data extracted from hospital records

- Sex
- Date of birth
- Date of intervention
- Valve position
- Type of prosthetic valve
- Previous valve replacement in the same valve position
- Preoperative logistic EuroSCORE I
- Valve-related events*
  - Cerebrovascular accident
  - Myocardial infarction
  - Vascular injury
  - Reexploration for bleeding
  - Other postoperative bleeding
  - Acute kidney injury
  - Atrial fibrillation
  - Pacemaker implantation
  - Structural valve deterioration
  - Non-structural dysfunction
  - Valve thrombosis
  - Thromboembolism
  - Bleeding
  - Endocarditis
- Reoperation

*For SAVR and SPVR patients, the occurrence of valve-related events during follow-up was extracted from their hospital records in the Erasmus MC, where the valve replacement was performed, and in referring hospitals. For TAVI patients, we only had access to the hospital records of the postintervention in-hospital period after the intervention at the Leiden University Medical Center, where the TAVI was performed. Therefore, only short-term complications were extracted for these patients.

Comparisons with general population

EQ-5D-5L utilities of patients were compared with utilities from the Dutch age and sex-matched general population by comparing the means and standard deviations.[1] For every patient in the patient population, the mean utility of persons from the general population with the same age and sex was extracted from the Dutch general population.[1] The mean of all of these extracted utilties represented the utility of the age and sex-matched general population.

The physical dimensions of the SF-12 were combined into a physical component score (PCS) and the mental dimensions into a mental component score (MCS) ranging from 0 (poor health) to 100 (perfect health) using domain weights derived with orthogonal rotation in a Dutch population.[2, 3] SF-12 dimensions and PCS and MCS scores were compared to the general population using norm-based scoring.2 Norm-based scoring is achieved by performing linear transformations of the scores to achieve a mean of 50 and standard deviation of 10 in the general Dutch population adjusted for age by weighting the mean scores of the general population by the proportion of patients in the reported age groups: 16-40, 41-60, 61-70, and >70 years.[2, 4] Scores below 50 indicate that patients have poorer quality of life than the general population, and vice versa.

The proportion of the patients who used informal care and person characteristics of informal caregivers were compared to the Dutch age-matched general population by weighting the values in the Dutch general population by the proportion of patients in the reported age groups: <20, 20-30, 30-40, 40-50, 50-55, 55-65, 65-75, and >75 years old.[5, 6] The amount of informal care (hours/week) was compared with the Dutch sex-matched general population (age-specific estimates were not available) by weighting the values in the Dutch general population by the proportion of males and females in the patient population.[5] Labor participation and absenteeism of patients was compared with the Dutch age and sex-matched general population by weighting the values in the Dutch general population by the proportion of male and female patients in the reported age groups: 15-24, 25-34, 35-44, 45-54, 55-64, and 65-74 years old.[7, 8] In accordance with the time the questionnaires were filled in, we compared informal care utilization of SAVR and SPVR patients with data from the general population in 2016 and of TAVI patients with data from the general population in 2017. For absenteeism of paid work only data from 2016 was available.

Regression analysis of EQ-5D utilities

Methods

The EQ-5D utilities collected in this study will be used in a patient-level simulation model to estimate the cost-effectiveness of heart valve implantations.[10] To be able to estimate patient-specific utilities in this model, we have performed regression analyses for SAVR and TAVI patients separately, including patient and intervention characteristics as independent variables and the EQ-5D utility score as dependent variables. The distribution of EQ-5D utilities was left-skewed, i.e. there were many patients with high utilities and few patients with low utilities. Since right-skewed data are less problematic in statistical analysis than left-skewed data[11], utilities were transformed to utility decrements with simple linear transformation (utility decrement = 1 – utility). Since many patients (SAVR 39%; TAVI 12%) had a utility decrement of zero (corresponding to a full health status), we estimated a two-part model. The first part of the model uses a logistic regression to determine the probability of having a EQ-5D utility decrement of 0 (i.e. full health). The second part uses a generalized linear model (GLM) to predict the EQ-5D utility decrement in patients with a EQ-5D utility decrement above 0 (i.e. less than full health). The expected utility for a patient can be calculated by multiplying the predicted values form the first part of the model by the predicted values from the second part using the following formula: (P utility decrement of 0 * 1) + ((1-P utility decrement of 0) * (1-estimated utility decrement in GLM)). The influence of the covariates on utility was estimated for a specific patient by combining the logistic regression model and GLM using this formula. The appropriate family (gamma) and associated link (log) of the GLM were chosen by visual assessment of Q-Q and residuals vs. fitted plots. Continuous variables with non-linear relationships with EQ-5D utility were modeled with restricted cubic splines or multiple fractional polynomials, whichever resulted in the lowest Akaike information criterion.[3] However, restricted cubic splines with more than two knots were not accepted, because our dataset was relatively small.[12]

Supplemental tables

Table S1. Postoperative complications

	SAVR (n=663)*		TAVI (n=257)
Complications	Questionnaire current quality of life (n=633)	Questionnaire quality of life after late complication (n=30)	
CVA	4 (0.6)	0 (0.0)	11 (4.3)
Myocardial infarction	3 (0.5)	0 (0.0)	3 (1.2)
Vascular injury	0 (0.0)	0 (0.0)	32 (12.5)
Reexploration for bleeding	94 (14.8)	8 (26.7)	0 (0)
Other postoperative bleeding	6 (0.9)	0 (0.0)	38 (14.8)
Acute kidney injury	25 (3.9)	4 (13.3)	16 (6.2)
Atrial fibrillation (new-onset)	0 (0.0)	0 (0.0)	-
- Transient	165 (26.1)	4 (13.3)	-
- At discharge	42 (6.6)	6 (20.0)	-
Pacemaker implantation	12 (1.9)	2 (6.7)	34 (13.2)

Results presented as n (%). SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve implantation. CVA: cerebrovascular accident.*No postoperative complications after surgical pulmonary valve replacement.

Table S2. Age and sex of responders and non-responders

	Responders	Non-responders
SVR		
Age, mean±SD	66.6±14.0	64.1±17.5
Male, %	69.4	63.0
TAVI		
Age, mean±SD	82.6±7.3	83.1±6.7
Male, %	60.3	38.9

SVR: surgical valve replacement. TAVI: transcatheter aortic valve implantation.

Table S3. Patient and intervention characteristics of SVR patients with late complication during follow-up

	SVR with late complication
n	30
Age, mean/median (IQR)	69.2/70.0 (63.0-76.5)
Age, range	50.0-84.0
Age group, n (%)	
19-60 years	6 (20.0)
61-70 years	11 (36.7)
>70 years	13 (43.3)
Sex, n (%)	
Male	23 (76.7)
Female	7 (23.3)
Relationship status, n (%)	
Partner	24 (80.0)
No partner	6 (20.0)
Income, n (%)	
Income above median*	13 (43.3)
Income below median*	13 (43.3)
Education, n (%)	
High education†	13 (43.3)
Low education	17 (56.7)
Years since intervention, mean/median (IQR)	2.4/2.1 (1.1-3.8)
Valve position, n (%)	
Aortic	30 (100)
Pulmonary	0 (0)
Isolated or multiple valve replacement, n (%)	
Isolated valve replacement	3 (10.0)
Multiple valve replacement	27 (90.0)
Concomitant CABG, n (%)	
Concomitant CABG	7 (23.3)
No concomitant CABG	23 (76.7)
Valve type, n (%)	
Biological	13 (43.3)
Mechanical	17 (56.7)
Previous valve replacement, n (%)	
Previous valve replacement	26 (86.7)
No previous valve replacement	4 (13.3)
Logistic EuroSCORE, mean/median (IQR)	12.8/7.4 (4.5-16.2)
Late complication, n (%)	
Endocarditis (in-hospital treatment)	4 (13.3)
Stroke	11 (36.7)
TIA	15 (50.0)

SVR: surgical valve replacement. IQR: interquartile range. CABG: coronary artery bypass grafting.
TIA: transient ischemic attack. *Net household income >€2.500.
†More than 4 years high school or higher education.

Table S4. EQ-5D-5L frequencies of domain scores

Levels*		Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression
SAVR						
	n	626	625	622	628	625
	1	386 (61.7)	557 (89.1)	378 (60.8)	355 (56.5)	479 (76.6)
	2	122 (19.5)	44 (7.0)	133 (21.4)	166 (26.4)	100 (16.0)
	3	87 (13.9)	20 (3.2)	81 (13.0)	82 (13.1)	34 (5.4)
	4	30 (4.8)	3 (0.5)	22 (3.5)	21 (3.3)	11 (1.8)
	5	1 (0.2)	1 (0.2)	8 (1.3)	4 (0.6)	1 (0.2)
SPVR						
	n	26	26	26	26	26
	1	24 (92.3)	26 (100.0)	22 (84.6)	20 (76.9)	21 (80.8)
	2	1 (3.8)	0 (0.0)	4 (15.4)	5 (19.2)	4 (15.4)
	3	1 (3.8)	0 (0.0)	0 (0.0)	1 (3.8)	1 (3.8)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TAVI						
	n	245	245	244	245	245
	1	53 (21.6)	171 (69.8)	92 (37.7)	98 (40.0)	159 (64.9)
	2	69 (28.2)	31 (12.7)	64 (26.2)	84 (34.3)	53 (21.6)
	3	76 (31.0)	22 (9.0)	54 (22.1)	42 (17.1)	29 (11.8)
	4	41 (16.7)	10 (4.1)	22 (9.0)	18 (7.3)	4 (1.6)
	5	6 (2.4)	11 (4.5)	12 (4.9)	3 (1.2)	0 (0.0)

Results presented as n (%). SAVR: surgical aortic valve replacement. SPVR: surgical pulmonary valve replacement. TAVI: transcatheter aortic valve implantation. *Higher level indicates poorer health-related quality of life.

Table S5. EQ-5D-3L utilities of patients and the matched general population

	Patients	General population
SAVR	0.850 ± 0.171	0.859 ± 0.040
SPVR	0.926 ± 0.123	0.914 ± 0.039
TAVI	0.731 ± 0.209	0.808 ± 0.035

Results presented as mean±standard deviation. SAVR: surgical aortic valve replacement. SPVR: surgical pulmonary valve replacement. TAVI: transcatheter aortic valve implantation.

Table S6. EQ-5D-5L frequencies of domain scores of patients with late complications

Levels*		Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression
All complications						
	n	29	29	29	29	28
	1	14 (48.3)	20 (69.0)	12 (41.4)	16 (55.2)	15 (53.6)
	2	4 (13.8)	2 (6.9)	8 (27.6)	8 (27.6)	6 (21.4)
	3	6 (20.7)	4 (13.8)	3 (10.3)	3 (10.3)	4 (14.3)
	4	2 (6.9)	2 (6.9)	4 (13.8)	1 (3.4)	2 (7.1)
	5	3 (10.3)	1 (3.4)	2 (6.9)	1 (3.4)	1 (3.6)
Stroke						
	n	11	11	11	11	11
	1	3 (27.3)	5 (45.5)	3 (27.3)	5 (45.5)	5 (45.5)
	2	1 (9.1)	1 (9.1)	3 (27.3)	4 (36.4)	3 (27.3)
	3	4 (36.4)	4 (36.4)	3 (27.3)	1 (9.1)	2 (18.2)
	4	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)
	5	2 (18.2)	5 (45.5)	1 (9.1)	5 (45.5)	5 (45.5)
TIA						
	n	14	14	14	14	13
	1	10 (71.4)	14 (100.0)	9 (64.3)	10 (71.4)	9 (69.2)
	2	3 (21.4)	14 (100.0)	4 (28.6)	3 (21.4)	3 (23.1)
	3	1 (7.1)	14 (100.0)	1 (7.1)	1 (7.1)	1 (7.7)
	4	10 (71.4)	14 (100.0)	9 (64.3)	10 (71.4)	9 (69.2)
	5	3 (21.4)	14 (100.0)	4 (28.6)	3 (21.4)	3 (23.1)
Endocarditis						
	n	4	4	4	4	4
	1	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)
	2	1 (25.0)	1 (25.0)	2 (50.0)	1 (25.0)	2 (50.0)
	3	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)
	4	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)
	5	1 (25.0)	1 (25.0)	2 (50.0)	1 (25.0)	2 (50.0)

Results presented as n (%). TIA: transient ischemic attack. *Higher level indicates poorer health-related quality of life.

Table S7. Logistic regression model and GLM (gamma family and log link) of EQ-5D utility of SAVR patients

Logistic regression model of probability of utility 1 (n=557)*	Coefficient	Odds ratio (95%CI)	p-value
Intercept	-1.938	0.144 (0.033-0.620)	0.009
Age (RCS 18-65 years)	1.860	6.423 (2.060-20.022)	0.001
Age (RCS 65-75 years)	-0.453	0.636 (0.024-16.613)	0.786
Age (RCS >=75 years)	-1.989	0.137 (0.028-0.670)	0.014
Male	0.357	1.430 (0.944-2.165)	0.092
Years since intervention	0.143	1.154 (1.044-1.276)	0.005
Biological valve (compared to mechanical)	-0.318	0.728 (0.428-1.237)	0.240
Concomitant CABG	-0.179	0.836 (0.545-1.283)	0.412
Multiple valve replacement	-0.465	0.628 (0.336-1.175)	0.145
Reoperation	-0.139	0.870 (0.445-1.700)	0.684
Higher education	0.386	1.471 (1.006-2.153)	0.047
Partner	0.102	1.107 (0.719-1.706)	0.643
Generalized linear model (gamma family with log link) for estimate of utility below 1 (n=338)	**Coefficient**	**Exponetiated coefficient† (95%CI)**	**p-value**
Intercept	1.053	2.867 (1.739-4.726)	0.000
Age	-0.002	0.998 (0.990-1.007)	0.683
Male	0.056	1.057 (0.896-1.247)	0.510
Time since intervention (RCS <1.5 years)	0.052	1.053 (0.735-1.509)	0.779
Time since intervention (RCS 1.5-3.5 years)	0.169	1.184 (0.738-1.898)	0.484
Time since intervention (RCS >=3.5 years)	0.249	1.283 (0.978-1.683)	0.073
Biological valve (compared to mechanical)	0.110	1.116 (0.895-1.391)	0.330
Concomitant CABG	0.065	1.067 (0.891-1.279)	0.479
Multiple valve replacement	-0.006	0.994 (0.776-1.273)	0.964
Reoperation	0.267	1.306 (0.975-1.749)	0.074
Higher education	0.194	1.214 (1.033-1.427)	0.019
Partner	0.231	1.260 (1.063-1.493)	0.008
Change in utility for a specific patient	**Utility**	**Utility difference**	
Female of 67.7 years at the time of the intervention who underwent first SAVR with a mechanical valve, without concomitant CABG or multiple valve replacement, no higher education and no partner	0.733		
Age (+10 = 77.6 years)	0.718	-0.015	
Male	0.778	0.045	
Years since intervention (+1)	0.745	0.012	
Years since intervention (+4)	0.803	0.070	
Concomitant CABG	0.736	0.003	
Multiple valve replacement	0.695	-0.038	
Biological valve	0.738	0.005	
Reoperation	0.787	0.054	
Higher education	0.809	0.076	
Partner	0.795	0.062	

RCS: restricted cubic spline. CI: confidence interval. n (%). TIA: transient ischemic attack. SAVR: surgical aortic valve replacement. CABG: coronary artery bypass grafting. *15 patients did not complete the EQ-5D and 61 patients had to be excluded from this analysis because valve type (n=8), education level (n=21) and/or having a partner yes or no (n=40) were missing. 240 patients (39.4%) had a utility of 1. †The exponentiated coefficient is the factor by which the arithmetic mean outcome on the original scale is multiplied. N.B. The results should be interpreted as follows, for example for sex: males are more likely to have a utility of 1 than females (logistic regression model) and when all other variables are equal, the mean estimated utility below 1 of males is 1.057 times (i.e. 5.7%) higher than for females (GLM).

Table S8. Logistic regression model and GLM (gamma family and log link) of EQ-5D utility of TAVI patients

Logistic regression model of probability of utility 1 (n=212)*	Coefficient	Odds ratio (95%CI)	p-value
Intercept	-2.600	0.074 (0.003-1.871)	0.114
Age (RCS <85 years)	-1.359	0.257 (0.002-28.546)	0.572
Age (RCS >85 years)	-0.407	0.666 (0.050-8.801)	0.757
Male	0.455	1.577 (0.587-4.233)	0.366
Years since intervention	-0.020	0.980 (0.707-1.360)	0.905
Transfemoral approach (vs. Transapical)	1.113	3.043 (0.573-16.145)	0.191
Partner	0.242	1.274 (0.493-3.288)	0.617
High education	-0.097	0.907 (0.369-2.231)	0.832
Generalized linear model (gamma family with log link) for estimate of utility below 1 (n=185)	**Coefficient**	**Exponetiated coefficient† (95%CI)**	**p-value**
Intercept	0.453	1.573 (0.600-4.122)	0.358
Age (RCS <80 years)	0.628	1.873 (1.096-3.203)	0.023
Age (RCS 80-85 years)	1.572	4.817 (0.648-35.818)	0.126
Age (RCS >85 years)	0.637	1.891 (0.877-4.078)	0.106
Male	0.185	1.203 (0.953-1.519)	0.121
Time since intervention (RCS <0.50 years)	0.102	1.107 (0.639-1.919)	0.718
Time since intervention (RCS 0.50-2 years)	-0.544	0.581 (0.313-1.078)	0.087
Time since intervention (RCS >2 years)	-0.554	0.575 (0.307-1.076)	0.085
Transfemoral approach (vs. Transapical)	-0.082	0.922 (0.691-1.228)	0.578
Partner	-0.042	0.959 (0.764-1.205)	0.721
High education	0.097	1.102 (0.891-1.362)	0.373
Change in utility for a specific patient	**Utility**	**Utility difference**	
Female of 82.6 years at t=0 who underwent transapical TAVI, no higher education and no partner	0.739		
Age (mean+10 = 92.6)	0.768	0.028	
Male	0.788	0.048	
Years since intervention (+1)	0.682	-0.057	
Years since intervention (+4)	0.671	-0.069	
Transfemoral	0.736	-0.003	
Higher education	0.763	0.023	
Partner	0.731	-0.008	

RCS: restricted cubic spline. CI: confidence interval. TAVI: transcatheter aortic valve implantation. *29 TAVI patients had to be excluded because education level (n=16) and/or having a partner yes or no (n=19) were missing. 29 patients (12%) had a utility of 1. †The exponentiated coefficient is the factor by which the arithmetic mean outcome on the original scale is multiplied. NB. The results should be interpreted as follows, for example for sex: males are more likely to have a utility of 1 than females (logistic regression model) and when all other variables are equal, the mean estimated utility below 1 of males is 1.203 times (i.e. 20.3%) higher than for females (GLM).

Table S9. SF-12-v2 dimension and summary component scores (norm-based using Dutch general population)

A. Norm based scores Netherlands (orthogonal rotation)[9]

	SAVR		SPVR		TAVI	
	n	mean ± SD	n	mean ± SD	n	mean ± SD
Physical functioning	568	43.2 ± 14.6	26	37.6 ± 18.5	206	40.3 ± 9.9
Role physical	582	48.4 ± 7.1	26	48.4 ± 6.9	216	46.0 ± 5.9
Bodily pain	623	55.3 ± 8.8	26	57.2 ± 6.0	237	51.7 ± 10.0
General health	628	43.8 ± 11.1	26	42.1 ± 13.4	238	41.8 ± 8.5
Vitality	606	47.9 ± 11.6	26	50.2 ± 12.3	227	45.2 ± 11.1
Social functioning	621	48.6 ± 11.5	26	47.2 ± 14.3	238	44.6 ± 10.8
Role emotional	583	49.8 ± 6.7	25	48.5 ± 7.0	218	47.5 ± 7.0
Mental health	601	50.4 ± 9.8	26	49.2 ± 10.0	223	49.1 ± 9.7
PCS	523	46.8 ± 11.5	25	44.7 ± 11.1	184	43.4 ± 8.5
MCS	523	50.2 ± 9.1	25	50.4 ± 9.8	184	48.2 ± 8.7

B. Raw scores

	SAVR		SPVR		TAVI	
	n	mean ± SD	n	mean ± SD	n	mean ± SD
Physical functioning	568	54.7 ± 32.6	26	70.2 ± 26.5	219	30.9 ± 29.3
Role physical	582	59.5 ± 27.0	26	75.5 ± 21.9	229	40.8 ± 25.1
Bodily pain	623	83.7 ± 22.2	26	92.3 ± 13.7	251	72.8 ± 26.9
General health	628	50.2 ± 22.0	26	58.7 ± 26.4	254	42.3 ± 17.9
Vitality	606	61.3 ± 23.9	26	70.2 ± 21.2	242	51.2 ± 25.1
Social functioning	621	76.7 ± 27.9	26	80.8 ± 27.7	254	61.8 ± 28.7
Role emotional	583	78.2 ± 23.8	25	79.0 ± 21.3	230	65.1 ± 26.7
Mental health	601	76.0 ± 18.2	26	76.4 ± 15.9	236	71.8 ± 19.2

C. Norm based scores US[9]

	SAVR		SPVR		TAVI	
	n	mean ± SD	n	mean ± SD	n	mean ± SD
Physical functioning	568	40.9 ± 11.2	26	46.2 ± 9.1	219	32.7 ± 10.1
Role physical	582	42.3 ± 10.0	26	48.1 ± 8.1	229	35.4 ± 9.3
Bodily pain	623	50.8 ± 9.1	26	54.3 ± 5.6	251	46.4 ± 11.0
General health	628	40.5 ± 9.5	26	44.2 ± 11.4	254	37.1 ± 7.7
Vitality	606	52.3 ± 9.6	26	55.9 ± 8.5	242	48.2 ± 10.1
Social functioning	621	47.2 ± 11.3	26	48.8 ± 11.2	254	41.1 ± 11.6
Role emotional	583	46.3 ± 10.6	25	46.7 ± 9.5	230	40.5 ± 12.0
Mental health	601	52.8 ± 8.9	26	53.1 ± 7.8	236	50.8 ± 9.3
PCS	523	41.6 ± 10.4	25	47.4 ± 8.0	184	34.4 ± 9.1
MCS	523	52.7 ± 9.8	25	51.8 ± 9.4	184	49.7 ± 10.1

SAVR: surgical aortic valve replacement. SPVR: surgical pulmonary valve replacement. TAVI: transcatheter aortic valve implantation. PCS: physical component score. MCS: mental component score. General population mean ± SD: 50 ± 10 Higher score indicates better health-related quality of life.

Table S10. SF-12-v2 dimension and summary component scores (norm-based using Dutch general population) of patients with late complications

	All complications		Stroke		TIA		Endocarditis	
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD
Physical functioning	26	42.3±30.6	8	40.6±32.6	14	48.2±31.7	4	25.0±20.4
Role physical	29	52.2±23.9	11	48.9±24.7	14	58.9±21.6	4	37.5±27.0
Bodily pain	29	79.3±27.6	10	75.0±33.3	15	85.0±22.8	4	68.8±31.5
General health	30	35.0±22.4	11	27.3±20.8	15	43.3±22.1	4	25.0±20.4
Vitality	29	51.7±26.7	10	57.5±26.5	15	53.3±22.9	4	31.2±37.5
Social functioning	29	67.2±25.1	11	63.6±25.9	14	75.0±21.9	4	50.0±28.9
Role emotional	29	69.4±28.1	11	68.2±21.2	14	75.0±30.6	4	53.1±35.9
Mental health	29	66.4±22.7	10	65.0±21.9	15	70.8±22.0	4	53.1±27.7
PCS	24	42.5±10.6	7	41.8±8.6	13	44.9±10.7	4	35.9±13.2
MCS	24	47.7±10.9	7	49.9±7.7	13	48.9±10.4	4	40.2±16.2

TIA: transient ischemic attack. PCS: psychical component score. MCS: mental component score. General population mean±SD: 50±10. Higher score indicates better health-related quality of life.

Table S11. SF-6D frequencies of domains

Levels		Physical functioning	Role limitations	Social functioning	Pain	Mental health	Vitality
SAVR							
	n	601	591	621	623	606	606
	1	188 (31.3)	50 (8.5)	20 (3.2)	7 (1.1)	7 (1.2)	27 (4.5)
	2	276 (45.9)	35 (5.9)	40 (6.4)	23 (3.7)	25 (4.1)	72 (11.9)
	3	137 (22.8)	410 (69.4)	125 (20.1)	64 (10.3)	126 (20.8)	155 (25.6)
	4	-	96 (16.2)	128 (20.6)	181 (29.1)	169 (27.9)	303 (50.0)
	5	-	-	308 (49.6)	348 (55.9)	279 (46.0)	49 (8.1)
SPVR							
	n	26	26	26	26	26	26
	1	5 (19.2)	5 (19.2)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
	2	13 (50.0)	4 (15.4)	1 (3.8)	0 (0.0)	1 (3.8)	3 (11.5)
	3	8 (30.8)	12 (46.2)	4 (15.4)	1 (3.8)	4 (15.4)	3 (11.5)
	4	-	5 (19.2)	5 (19.2)	6 (23.1)	12 (46.2)	16 (61.5)
	5	-	-	15 (57.7)	19 (73.1)	9 (34.6)	4 (15.4)
TAVI							
	n	242	236	254	251	241	242
	1	131 (54.1)	7 (3.0)	13 (5.1)	6 (2.4)	4 (1.7)	18 (7.4)
	2	97 (40.1)	6 (2.5)	35 (13.8)	25 (10.0)	12 (5.0)	50 (20.7)
	3	14 (5.8)	217 (91.9)	86 (33.9)	46 (18.3)	71 (29.5)	88 (36.4)
	4	-	6 (2.5)	59 (23.2)	82 (32.7)	69 (28.6)	74 (30.6)
	5	-	-	61 (24.0)	92 (36.7)	85 (35.3)	12 (5.0)

Results presented as n (%). SAVR: surgical aortic valve replacement. SPVR: surgical pulmonary valve replacement. TAVI: transcatheter aortic valve implantation.

Table S12. SF-6D frequencies of domains of patients with late complications

Levels		Physical functioning	Role limitations	Social functioning	Pain	Mental health	Vitality
All complications							
	n	30	29	29	29	29	29
	1	11 (36.7)	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)	3 (10.3)
	2	15 (50.0)	3 (10.3)	4 (13.8)	2 (6.9)	3 (10.3)	5 (17.2)
	3	4 (13.3)	24 (82.8)	8 (27.6)	3 (10.3)	10 (34.5)	9 (31.0)
	4	-	1 (3.4)	10 (34.5)	8 (27.6)	6 (20.7)	11 (37.9)
	5	-	-	7 (24.1)	15 (51.7)	10 (34.5)	1 (3.4)
Stroke							
	n	11	11	11	10	10	10
	1	1 (3.0)	27 (1.0)	9 (0.0)	0 (1.0)	10 (0.0)	0 (1.0)
	2	2 (6.0)	55 (1.0)	9 (2.0)	18 (0.0)	0 (0.0)	0 (1.0)
	3	3 (2.0)	18 (9.0)	82 (3.0)	27 (2.0)	20 (5.0)	50 (2.0)
	4	-	0 (0.0)	0 (4.0)	36 (2.0)	20 (3.0)	30 (6.0)
	5	-	-	0 (2.0)	18 (5.0)	50 (2.0)	20 (0.0)
TIA							
	n	15	14	14	15	15	15
	1	5 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	8 (53.3)	2 (14.3)	0 (0.0)	1 (6.7)	1 (6.7)	4 (26.7)
	3	2 (13.3)	11 (78.6)	5 (35.7)	1 (6.7)	4 (26.7)	6 (40.0)
	4	-	1 (7.1)	4 (28.6)	4 (26.7)	3 (20.0)	4 (26.7)
	5	-	-	5 (35.7)	9 (60.0)	7 (46.7)	1 (6.7)
Endocarditis							
	n	4	4	4	4	4	4
	1	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)
	2	1 (25.0)	0 (0.0)	2 (50.0)	1 (25.0)	2 (50.0)	0 (0.0)
	3	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)
	4	-	0 (0.0)	2 (50.0)	2 (50.0)	0 (0.0)	1 (25.0)
	5	-	-	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)

Results presented as n (%). TIA: transient ischemic attack.

Table S13. Visual analogue scale (VAS) and utilities based on EQ-5D-5L and SF-6D of patients with late complications

	All complications		Stroke		TIA		Endocarditis	
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD
VAS	26	64.7±21.2	9	60.6±20.5	13	73.6±16.5	4	45.0±25.2
EQ-5D	28	0.697±0.348	11	0.629±0.304	13	0.879±0.223	4	0.294±0.452
SF-6D	26	0.696±0.122	9	0.699±0.088	13	0.726±0.124	4	0.591±0.155

TIA: transient ischemic attack.

Table S14. Informal care in patients with late complications

		Hours per week
Informal care during four weeks after complication		
Informal care received	8 (26.7)	43.1 ± 56.7
Endocarditis	1 (25.0)	
Stroke	5 (45.5)	
TIA	2 (13.3)	
Type of informal care		
Household activities	4 (13.3)	13.8 ± 17.9
Personal care	4 (13.3)	71.0 ± 85.8
Practical support	4 (13.3)	11.3 ± 2.3
Total duration of informal care, years	1.1 ± 1.9	
Costs per week, €		
All patients	149 ± 462	
Patients who received informal care	618 ± 812	
Patient characteristics		
Age, years	74.4 ± 9.8	
Sex		
Male	7 (87.5)	
Female	1 (12.5)	
Informal caregiver characteristics		
Age, years	70.8 ± 10.5	
Sex		
Male	1 (12.5)	
Female	7 (87.5)	
Relationship with patient		
Partner	8 (100.0)	

Results presented as mean±standard deviation or n (%). TIA: transient ischemic attack.

Table S15. Productivity in patients with late complications

Paid work after complication	All complications	Endocarditis	Stroke	TIA
Change in employment after complication				
No paid work before or after intervention	20 (66.7)	2 (50.0)	8 (72.7)	10 (66.7)
Quit	2 (6.7)	1 (25.0)	0 (0.0)	1 (6.7)
Less	2 (6.7)	1 (25.0)	1 (9.1)	0 (0.0)
Same	5 (16.7)	0 (0.0)	2 (18.2)	3 (20.0)
More	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Started working after intervention	1 (3.3)	0 (0.0)	0 (0.0)	1 (6.7)
Paid work four weeks after complication				
Absenteeism				
Yes	2 (25.0)	0 (0.0)	2 (66.7)	0 (0.0)
No	4 (50.0)	0 (0.0)	0 (0.0)	4 (100.0)
Missing	2 (25.0)	1 (100.0)	1 (33.3)	0 (0.0)
Days during the past four weeks	20.0 ± 0.0	-	20.0 ± 0.0	-
Presenteeism				
Yes	1 (12.5)	0 (0.0)	1 (33.3)	0 (0.0)
No	4 (50.0)	0 (0.0)	0 (0.0)	4 (100.0)
Missing	3 (37.5)	1 (100.0)	2 (66.7)	0 (0.0)
Days during the past four weeks	40.0 ± -	-	40.0 ± -	-
Productivity*	5.0 ± -	-	5.0 ± -	-
Unpaid work last four weeks				
Yes	11 (36.7)	0 (0.0)	4 (36.4)	7 (46.7)
No	15 (62.5)	4 (100.0)	4 (36.4)	7 (77.8)
Missing	4 (44.4)	0 (0.0)	3 (27.3)	1 (6.7)
Productivity				
Less unpaid work	5 (45.5)	-	4 (100.0)	1 (14.3)
Days during the past four weeks	26.3 ± 3.5	-	26.3 ± 3.5	-
Hours/day during the past four weeks	4.2 ± 3.6	-	5.0 ± 3.6	1.0 ± -

Results presented as mean±standard deviation or n (%). TIA: transient ischemic attack.

References supplemental material

1. Versteegh MM, Vermeulen KM, Evers SM, de Wit GA, Prenger R and Stolk EA. Dutch tariff for the five-level version of EQ-5D. *Value in health*. 2016;19:343-352.
2. Ware JE, Kosinski M and Turner-Bowker D. User's Manual for the SF-12v2™ Health Survey with a Supplement Documenting SF-12® Health SurveyQualityMetric Incorporated. 2001.
3. Mols F, Pelle AJ and Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Qual Life Res*. 2009;18:403-414.
4. Aaronson NK, Muller M, Cohen PD, Essink-Bot M-L, Fekkes M, Sanderman R, Sprangers MA, te Velde A and Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *Journal of clinical epidemiology*. 1998;51:1055-1068.
5. Centraal Bureau voor de Statistiek (CBS). Gezondheid en zorggebruik; persoonskenmerken 2016-2017. 2018.
6. Centraal Bureau voor de Statistiek (CBS). Leefstijl en (preventief) gezondheidsonderzoek; persoonskenmerken 2016. 2017.
7. Centraal Bureau voor de Statistiek (CBS). Ziekteverzuim volgens werknemers; geslacht en leeftijd 2016. 2017.
8. Centraal Bureau voor de Statistiek (CBS). Arbeidsdeelname; kerncijfers. 2018.
9. Ware JE, Kosinski M, Turner-Bowker DM and Gandek B. *How to score version 2 of the SF-12 health survey (with a supplement documenting version 1)*: QualityMetric Incorporated Lincoln, RI; 2005.
10. Huygens SA, Rutten-van Mölken MPMH, Bekkers JA, et al. Conceptual model for early health technology assessment of current and novel heart valve interventions. *Open Heart* 2016;**3**:e000500.
11. Wolowacz SE, Briggs A, Belozeroff V, et al. Estimating health-state utility for economic models in clinical studies: an ISPOR good research practices task force report. *Value in Health* 2016;**19**:704-19.
12. Steyerberg EW. *Clinical prediction models: a practical approach to development, validation, and updating*. Springer Science & Business Media 2008

7

How much does a heart valve implantation cost and what are the health care costs afterwards?

Simone A. Huygens, Lucas M.A. Goossens, Judith A. van Erkelens,
Johanna J.M. Takkenberg, Maureen P.M.H. Rutten-van Mölken.

Open Heart. 2018;5:e000672

ABSTRACT

Objective: In the era of limited healthcare budgets, healthcare costs of heart valve implantations need to be considered to inform cost-effectiveness analyses. We aimed to provide age group-specific costs estimates of heart valve implantations, related complications, and other healthcare utilisation following the intervention.

Methods: We performed retrospective analyses of healthcare costs of patients who had undergone heart valve implantations in 2010-2013 and controls using claims data from Dutch health insurers. Heart valve implantations included surgical valve replacement and transcatheter valve implantation in all heart valve positions. Patients were divided in four age groups. Control groups were created by taking random samples of the Dutch population stratified by age, gender, socioeconomic status, and comorbidities. We applied non-parametric bootstrapping to address uncertainty of the cost estimates. The association of patient and intervention characteristics with costs was determined by (multilevel) generalized linear models.

Results: The baseline characteristics of 18,903 patients and 188,925 controls were comparable. The annual healthcare costs were substantially higher for surgical heart valve replacement patients than for controls, especially in the year of heart valve implantation. Factors associated with increased annual healthcare costs for patients were older age, female gender, comorbidities, low socioeconomic status, and complications.

Conclusions: We provided a comprehensive overview of age group-specific incidence of heart valve implantations, subsequent survival and complications as well as associated healthcare costs of all patients in the Netherlands. Our results provide real-world costs estimates that can be used as a benchmark for costs of future innovative heart valve implantations.

INTRODUCTION

Heart valve disease has a profound impact on the use and costs of healthcare. This impact is even greater for heart valve disease than for coronary heart disease, despite the higher prevalence of coronary heart disease.[1] In developed countries, the prevalence of heart valve disease is 2.5%, and this prevalence is the highest in patients aged ≥75 years(13.3%).[2] Due to an ageing population, the number of patients with heart valve disease requiring valve replacement is expected to rise, reaching more than 800,000 annual procedures worldwide by 2050.[3] As a result, healthcare expenditures and societal burden of heart valve disease will increase.

In patients with severe heart valve disease, replacement of the native valve with a heart valve substitute may be required. There are different effective options, but every heart valve substitute type also has its limitations.[4] In the future, these limitations may be reduced with the many emerging technologies in the field of heart valve interventions, such as tissue-engineered heart valves and less invasive implantation methods. Before these new technologies can be introduced in clinical practice, it is important to establish that they are effective and cost-effective, considering the scarcity of resources for healthcare. To determine whether a new intervention is cost-effective, the costs and effects of the new intervention need to be compared with current care. Since the choice of heart valve implantation and its outcomes differs substantially among age groups [5], it is likely that healthcare costs will also be influenced by patients' age. Hence, having robust age group-specific estimates of the costs of current care is important.

The objective of this study was to estimate the costs of currently used heart valve implantations and also costs of complications as well as healthcare use outside hospitals in the years after heart valve implantations in different age groups. We estimated these costs by retrospective analyses of health insurance claims of patients who had undergone heart valve implantations. This provides valuable real-world age group-specific cost estimates of all costs associated with heart valve implantations, in comparison with previous studies that focused on costs of the heart valve implantation and short-term follow-up in specific age groups only.[6, 7]

METHODS

Patients

We used health insurance claims databases ("Vektis") which contain the healthcare expenditures of all the insured in the Netherlands, which is 99% of all Dutch residents (±17 million people). Patients were selected using Diagnosis Related Group (DRG) codes of heart

valve implantations (Table S1). We could distinguish DRG codes for isolated or multiple surgical heart valve replacement (SVR) and transcatheter heart valve implantation (TVI) in every heart valve position with or without concomitant procedures. In the pulmonary and tricuspid valve position, DRG codes did not distinguish between valve repair and replacement, therefore patients who have undergone repairs in these valve positions are also included in our patient population.

We used data from Vektis for the years 2010-2013. Data before 2010 are generally considered less valid. On the date of data extraction for this study (January 2016), data from the years 2014 and further were incomplete due to time lags in administrations. Before 2013, there was no specific DRG code for TVI, therefore we could only include TVI patients in the year 2013.

Controls

To calculate excess healthcare costs due to the heart valve implantation, we compared annual healthcare costs of the patient group with a control group. The control group was created by stratified sampling from the remainder of the Dutch insured population in the Vektis databases to ensure that the distributions of person characteristics across the strata were similar to that in the patient population. The control group was ten times as large as the patient population. Strata were based on age class, gender, socioeconomic status (SES), and comorbidities. Age was divided into nine age classes: 0-1, 2-18, 19-30, 31-40, 41-50, 51-60, 61-70, 71-80, and >80 years. SES was based on status scores reflecting the SES of a district based on characteristics of its residents: education, income, and position on the labour market.[8] The status scores were divided in four groups based on percentiles, with lower percentiles representing lower SES. Comorbidities were based on Pharmacy Cost Groups, which is an outpatient morbidity measure based on prior use of prescribed drugs as marker for chronic conditions.[9] The strata used for comorbidities differed per age class because of differences in prevalence of comorbidities (see Supplementary Material).

Healthcare costs

Patients were followed over time from the opening date of the heart valve implantation DRG in the financial administrative system until death or until 31 December 2013, whichever occurred first, to assess whether they experienced complications after the heart valve implantation and to collect their other healthcare costs besides the costs of heart valve implantation itself.

For every patient, the costs of the initial heart valve implantation and the healthcare costs during the first postintervention year and subsequent (max. 4) years were determined. Costs were defined as expenditures reimbursed by health insurers and expressed in euros (€). The procedure costs included the costs of the DRG and intensive care unit (ICU) stay. We

assumed that the costs of ICU stay in the first postintervention year excluding the ICU costs related to specific complications were related to the heart valve implantation.

Complications were extracted from the Vektis database using DRG codes for treatment of complications (Table S2). The complications of interest were based on the conceptual model we have developed previously.[5] The following complications were available in the Vektis database: acute kidney injury, atrial fibrillation (AF), stroke, transient ischemic attack, prosthetic valve endocarditis (conservative treatment), myocardial infarction, pacemaker implantation, and re-intervention (redo heart valve implantation). For every complication, costs (DRG+ICU costs), proportions of patients admitted to the ICU, and number of ICU days were determined.

For both patients and controls, annual healthcare costs were determined. The starting point of the calculation of annual healthcare costs of patients is the quarter in which the heart valve implantation was performed. The annual healthcare costs were classified into costs of general practitioners, specialised medical care (both inpatient and outpatient care, including costs of DRGs, ICU stay, medicines on the expensive drugs list, primary care diagnostics, and other costs), pharmaceuticals, paramedical care, patient transport, home care, nursing homes, and geriatric rehabilitation care. Cost of medicines on the expensive drug list, home care, nursing homes and geriatric rehabilitation care were only available in the Vektis database from the year 2012 onwards.

Statistical analysis

The statistical analyses were performed with SAS 9.4 using SAS Enterprise Guide 7.1.

Descriptive analyses

Patients and controls were divided in four age groups: children (0-18 years), young adults (19-60 years), middle aged (61-70 years) and elderly patients (>70 years). For every age group, we performed descriptive analyses of person and intervention characteristics, occurrence of complications, and healthcare costs. Continuous variables were depicted as means and standard deviations (SD) or 95% confidence intervals (CI) and discrete variables as counts and proportions. We assessed survival after SVR and TVI using Kaplan-Meier estimates. The difference between mean healthcare costs of patients and controls was calculated; mean costs of controls were based on the same calendar years as patients (e.g. for patients postintervention year 2 could be between 2011 and 2013; therefore these costs were compared to the average costs of controls in 2011-2013). As the cost data were skewed, non-parametric bootstrapping (2000 replications) was used to address uncertainty (with 95% CI based on 2.5th and 97.5th percentile) in the annual healthcare costs. To be able to report annual healthcare costs, only patients who were followed the entire year of interest (including patients who died during this year) were included in these analyses.

Association analyses

To estimate the association between healthcare costs and patient and intervention characteristics, we developed (multilevel) generalized linear models ((M)GLM) for intervention, complication and annual healthcare costs. For annual healthcare costs of patients after heart valve implantations, we estimated a MGLM for children and for adults with normal distributions and identity links, and with several observation periods per patient. All patients with at least 1-year complete follow-up were included. We excluded patients with incomplete follow-up in the first postintervention year (except for patients who died) to avoid overestimation of costs per day in postintervention year 1 due to the high costs in the period after the intervention. To correct for differences in total duration of follow-up, the total healthcare costs were divided by the follow-up duration to estimate average costs per day during the specific year. The independent variables included in the MGLMs for children and adults were time (i.e. intervention period (no defined length; includes costs of heart valve implantation and ICU stay), remaining postintervention year 1, and postintervention year 2, 3, and 4), gender, and SES. In addition, the model of adults included age groups, comorbidities, mortality, and complications. Mortality and the occurrence of complications were time dependent. Comorbidities, mortality and the occurrence of complications were not included in the model for children because there were no children with comorbidities and only a small proportion of children who experienced complications (including mortality). Details about the GLMs in which the costs of interventions and complications were analysed separately can be found in the Supplementary Material.

RESULTS

Study population

In total, we included 18,903 patients (SVR: n=17,991. TVI: n=912) and 188,925 controls. The baseline characteristics of patients and controls were comparable (Table 1). The mean (median) follow-up was 1.9 (1.9) and 0.4 (0.4) years for SVR and TVI patients, respectively. Figure 1 illustrates the Kaplan-Meier survival curves after SVR and TVI. During follow-up, 41 children (10.0%), 841 young adults (26.2%), 1,424 middle aged patients (29.5%), and 3,036 elderly patients (31.9%) experienced one or more complications after SVR. After TVI, six young adults (18.2%), two middle aged (2.9%), and 157 elderly patients (19.4%) experienced complications.

Table 2 presents the occurrence of complications per postintervention year, the proportion of patients with ICU stay and the mean length of ICU stay after complications.

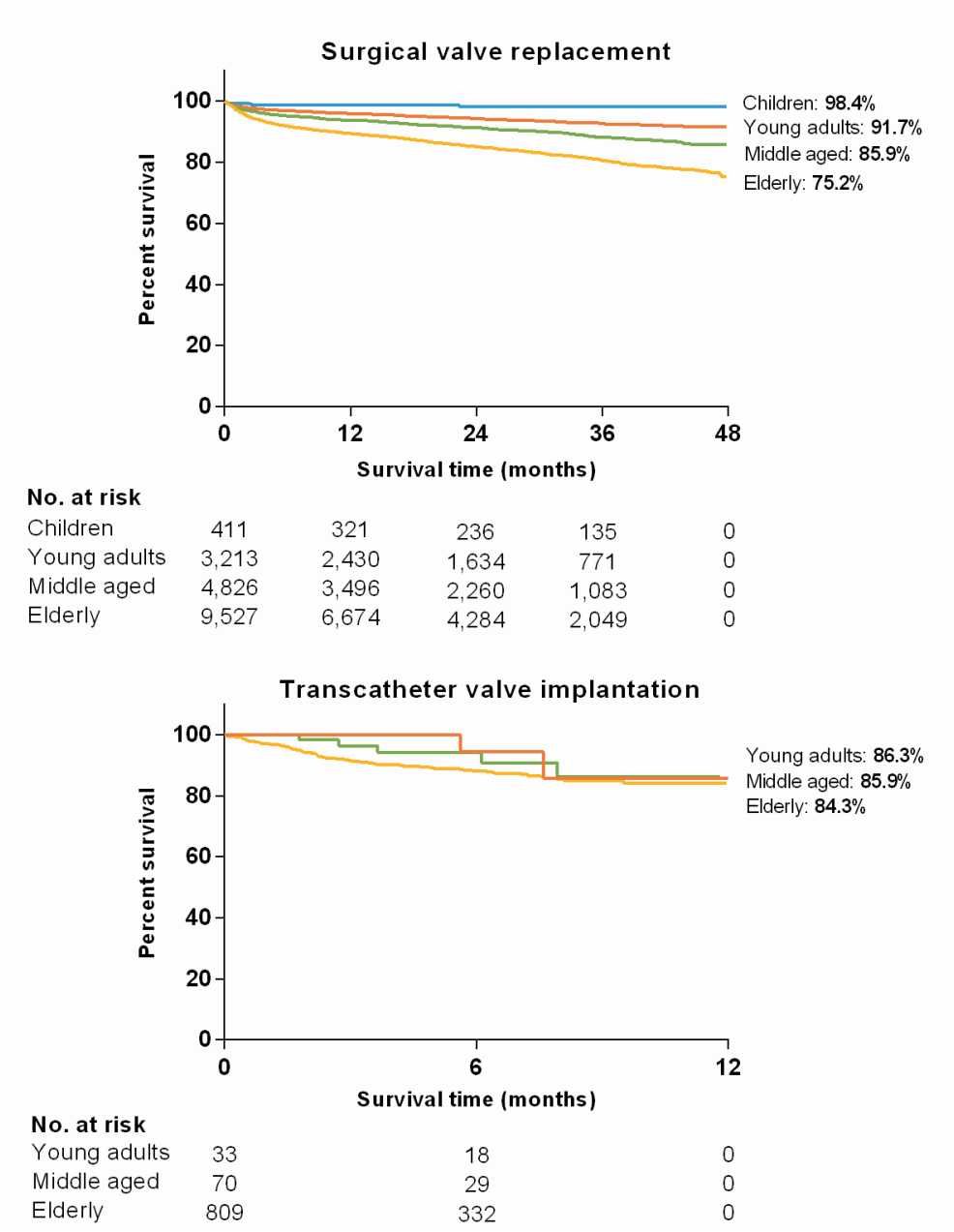


Figure 1. Kaplan-Meier curves of survival after SVR (top) and TVI (bottom) divided by age group.

Table 1. Person and intervention characteristics of patients and controls divided by age group

	Children (0-18 years)		Young adults (19-60 years)			Middle aged (61-70 years)			Elderly (>70 years)		
	Patients	Controls	Patients		Controls	Patients		Controls	Patients		Controls
	SVR		SVR	TVI		SVR	TVI		SVR	TVI	
Number of persons[1]	411	4170	3,213 (99.0)	33 (1.0)	33,960	4,826 (98.6)	70 (1.4)	50,440	9,527 (92.2)	809 (7.8)	10,0355
Follow-up in years[2]	2.2±1.2	<4.0	2.0±1.2	0.5±0.3	<4.0	1.9±1.2	0.4±0.3	<4.0	1.8±1.2	0.4±0.3	<4.0
Age at time of intervention, mean±SD, range	5.5±6.2		50.3±9.4	39.4±14.9	-	66.0±2.8	66.9±2.1	-	77.6±4.4	81.9±4.9	-
	0-18	0-18	19-60	19-60	19-60	61-70	62-70	61-70	71-94	71-95	>70
Male	245 (59.6)	2,490 (59.7)	2,140 (66.6)	23 (69.7)	22,730 (66.9)	3,261 (67.6)	43 (61.4)	33,770 (67.0)	5,075 (53.3)	387 (47.8)	47,580 (47.4)
Socioeconomic status[3]											
0-20	72 (17.5)	720 (17.3)	737 (22.9)	4 (12.1)	7,650 (22.5)	987 (20.5)	23 (32.9)	10,530 (20.9)	2,042 (21.4)	202 (25.0)	21,780 (21.7)
21-40	80 (19.5)	810 (19.4)	681 (21.2)	6 (18.2)	7,250 (21.3)	994 (20.6)	12 (17.1)	10,310 (20.4)	2,031 (21.3)	161 (19.9)	21,280 (21.2)
41-70	124 (30.2)	1,250 (30.0)	897 (27.9)	11 (33.3)	9,570 (28.2)	1,587 (32.9)	16 (22.9)	16,490 (32.7)	2,984 (31.3)	228 (28.2)	31,180 (31.1)
71-100	135 (32.8)	1,390 (33.3)	888 (27.6)	12 (36.4)	9,380 (27.6)	1,256 (26.0)	19 (27.1)	13,090 (26.0)	2,469 (25.9)	218 (26.9)	26,110 (26.0)
Comorbidities											
COPD, DM, kidney disease and/or HF			780 (24.3)	9 (27.3)	8,510 (25.1)	2,086 (43.2)	47 (67.1)	22,160 (43.9)	5,041 (52.9)	518 (64.0)	54,145 (54.0)
Hypertension			1,106 (34.4)	6 (18.2)	11,600 (34.2)	1,659 (34.4)	17 (24.3)	17,330 (34.4)	3,036 (31.9)	199 (24.6)	31,310 (31.2)
Other comorbidities			293 (9.1)	3 (9.1)	3,170 (9.3)	416 (8.6)	3 (4.3)	4,210 (8.3)	575 (6.0)	36 (4.4)	5,880 (5.9)
No comorbidities	411 (100.0)	4,170 (100.0)	1,034 (32.2)	15 (45.5)	10,680 (31.4)	665 (13.8)	3 (4.3)	6,740 (13.4)	875 (9.2)	56 (6.9)	9,020 (9.0)
Valve position											
Aortic	29 (7.1)		2,460 (76.6)	6 (18.2)		4,133 (85.6)	25 (35.7)		8,578 (90.0)	395 (48.8)	
Pulmonary	338 (82.2)		115 (3.6)			2 (0.0)			2 (0.0)		
Mitral	19 (4.6)		431 (13.4)	2 (6.1)		484 (10.0)	1 (1.4)		652 (6.8)		
Tricuspid	23 (5.6)		65 (2.0)			34 (0.7)			36 (0.4)		
Aortic and mitral	2 (0.5)		142 (4.4)			173 (3.6)			259 (2.7)		
Unknown				25 (75.8)			44 (62.9)			414 (51.2)	

Table 1. Continued

	Children (0-18 years)		Young adults (19-60 years)			Middle aged (61-70 years)			Elderly (>70 years)		
	Patients	Controls	Patients		Controls	Patients		Controls	Patients		Controls
	SVR		SVR	TVI		SVR	TVI		SVR	TVI	
Concomitant procedures											
No concomitant procedures	214 (52.1)		1,924 (59.9)	33 (100.0)		2,485 (51.5)	70 (100.0)		4,735 (49.7)	807 (99.8)	
CABG			407 (12.7)			1,364 (28.3)			3,409 (35.8)	2 (0.2)	
Valve repair	1 (0.2)		253 (7.9)			344 (7.1)			643 (6.7)		
Maze + CABG or valve repair			58 (1.8)			212 (4.4)			418 (4.4)		
Bentall	8 (1.9)		303 (9.4)			162 (3.4)			94 (1.0)		
Aortic ascendens			173 (5.4)			161 (3.3)			114 (1.2)		
Tetralogy of Fallot	187 (45.5)		6 (0.2)								
Aortic ascendens + valve repair			27 (0.8)			31 (0.6)			36 (0.4)		
HOCM			11 (0.3)			14 (0.3)			52 (0.5)		
Aortic root			24 (0.7)			19 (0.4)			8 (0.1)		
Aortic root + CABG			17 (0.5)			17 (0.4)			13 (0.1)		
Left ventricle repair	1 (0.2)		10 (0.3)			17 (0.4)			5 (0.1)		

Results presented as mean±standard deviation or n (%). SVR: surgical valve replacement. TVI: transcatheter valve implantation. SD: standard deviation. COPD: Chronic Obstructive Pulmonary Disease. DM: diabetes mellitus. HF: heart failure. CABG: concomitant coronary artery bypass grafting. HOCM: Hypertrophic Obstructive Cardiomyopathy. [1]14 patients excluded because their age was unknown. [2]Control group includes patients who died during the study period, but information on number of deaths or follow-up of controls was not available. [3]Higher percentiles represent higher SES.

Table 2. Complications after initial heart valve intervention

	No. of patients with complications*, n (% of total patients)					ICU stay, n (% of patients with complication)		ICU stay in days, mean±SD	
	Year 1		Year 2	Year 3	Year 4	Year 1-4		Year 1-4	
	SVR	TVI	SVR	SVR	SVR	SVR	TVI	SVR	TVI
Children (0-18 years) (n)	411	0	406	405	405				
All-cause mortality	5 (1.2)		1 (0.2)						
Complications (total)	25 (6.1)		12 (3.0)	4 (1.0)	2 (0.5)	16 (39.0)			
AKI	2 (0.5)					1 (50.0)		2.0±-	
AF	4 (1.0)		3 (0.7)		1 (0.2)				
Stroke			1 (0.2)						
TIA									
Endocarditis	4 (1.0)		2 (0.5)						
MI									
PI	1 (0.2)		1 (0.2)	2 (0.5)					
Re-intervention	14 (3.4)		5 (1.2)	2 (0.5)	1 (0.2)	15 (68.2)		2.1±1.1	
Young adults (19-60 years) (n)	3,213	33	3,090	3,056	3,034				
All-cause mortality	123 (3.8)	2 (6.1)	34 (1.1)	22 (0.7)	5 (0.2)				
Complications (total)	680 (21.2)	6 (18.2)	189 (6.1)	98 (3.2)	37 (1.2)	130 (15.5)	3 (50.0)		
AKI	26 (0.8)		6 (0.2)	1 (0.0)	1 (0.0)	6 (18.2)		13.5±18.6	
AF	268 (8.3)	1 (3.0)	63 (2.0)	40 (1.3)	17 (0.6)	8 (2.4)		2.0±2.4	
Stroke	154 (4.8)		40 (1.3)	18 (0.6)	4 (0.1)	26 (12.8)		10.4±21.4	
TIA	51 (1.6)		29 (0.9)	14 (0.5)	2 (0.1)	1 (1.2)		2.0±-	
Endocarditis	118 (3.7)	2 (6.1)	37 (1.2)	15 (0.5)	8 (0.3)	29 (18.2)	1 (50.0)	5.0±4.0	2.0±-
MI	25 (0.8)		8 (0.3)	4 (0.1)	1 (0.0)	5 (13.5)		17.8±32.6	
PI	90 (2.8)	2 (6.1)	10 (0.3)	9 (0.3)	1 (0.0)	11 (10.1)		3.7±2.5	
Re-intervention	39 (1.2)	2 (6.1)	18 (0.6)	6 (0.2)	3 (0.1)	41 (65.1)	2 (100.0)	9.1±26.6	8.5±4.9

Table 2. Continued

	No. of patients with complications*, n (% of total patients)					ICU stay, n (% of patients with complication)		ICU stay in days, mean±SD	
	Year 1		Year 2	Year 3	Year 4	Year 1-4		Year 1-4	
	SVR	TVI	SVR	SVR	SVR	SVR	TVI	SVR	TVI
Middle aged (61-70 years) (n)	4,826	70	4,545	4,472	4,413				
All-cause mortality	281 (5.8)	5 (7.1)	73 (1.6)	59 (1.3)	15 (0.3)				
Complications (total)	1,167 (24.2)	2 (2.9)	300 (6.6)	176 (3.9)	67 (1.5)	153 (10.7)	1 (50.0)		
AKI	57 (1.2)		17 (0.4)	5 (0.1)	2 (0.0)	10 (12.7)		8.3±7.0	
AF	534 (11.1)		138 (3.0)	87 (1.9)	31 (0.7)	10 (1.6)		2.7±2.2	
Stroke	259 (5.4)		53 (1.2)	27 (0.6)	11 (0.2)	43 (12.9)		5.8±5.1	
TIA	113 (2.3)		41 (0.9)	32 (0.7)	10 (0.2)	8 (4.3)		3.9±2.0	
Endocarditis	153 (3.2)		33 (0.7)	17 (0.4)	4 (0.1)	29 (15.7)		7.0±9.4	
MI	45 (0.9)		16 (0.4)	9 (0.2)	2 (0.0)	8 (11.4)		7.6±7.4	
PI	158 (3.3)	1 (1.4)	27 (0.6)	12 (0.3)	7 (0.2)	14 (7.0)		11.4±22.3	
Re-intervention	49 (1.0)	1 (1.4)	10 (0.2)	5 (0.1)	5 (0.1)	28 (41.2)	1 (100.0)	4.5±6.3	1.0±-
Elderly (>70 years) (n)	9,527	809	8,580	8,315	8,146				
All-cause mortality	947 (9.9)	87 (10.8)	265 (3.1)	169 (2.0)	61 (0.7)				
Complications (total)	2,436 (25.6)	157 (19.4)	678 (7.9)	426 (5.1)	125 (1.5)	339 (11.2)	18 (11.5)		
AKI	135 (1.4)	8 (1.0)	14 (0.2)	9 (0.1)		29 (18.4)		15.0±15.5	
AF	994 (10.4)	26 (3.2)	340 (4.0)	211 (2.5)	67 (0.8)	33 (2.6)	1 (3.8)	6.9±13.1	2.0±-
Stroke	670 (7.0)	33 (4.1)	155 (1.8)	87 (1.0)	19 (0.2)	114 (12.9)		6.5±6.4	
TIA	220 (2.3)	11 (1.4)	66 (0.8)	52 (0.6)	13 (0.2)	11 (3.3)		2.8±1.5	
Endocarditis	184 (1.9)	8 (1.0)	57 (0.7)	23 (0.3)	9 (0.1)	36 (14.3)		8.9±9.9	
MI	112 (1.2)	5 (0.6)	33 (0.4)	22 (0.3)	7 (0.1)	18 (10.9)		4.4±4.8	
PI	428 (4.5)	57 (7.0)	67 (0.8)	47 (0.6)	13 (0.2)	42 (7.6)		4.9±4.6	
Re-intervention	76 (0.8)	35 (4.3)	9 (0.1)	11 (0.1)	2 (0.0)	54 (55.1)	16 (45.7)	7.8±17.8	3.2±5.9

SD: standard deviation. SVR: surgical valve replacement. TVI: transcatheter valve implantation. AKI: acute kidney injury. AF: atrial fibrillation. TIA: transient ischemic attack. MI: myocardial infarction. PI: pacemaker implantation. ICU: intensive care unit. *Early complications are included in intervention DRG and therefore not included here.

Healthcare costs – descriptive analyses

Table 3 and Figure 2 summarise the costs of heart valve implantations, complications and total annual healthcare costs during the first three postintervention years divided by age group. These costs could not be determined for TVI patients because their follow-up was less than 1 year. The annual healthcare costs of patients were substantially higher than the costs of controls in all age groups, especially in the year of implantation (Figure 2; children €11,766 vs €796, young adults €15,060 vs €2,944, middle aged €16,104 vs €4,612, and elderly €18,255 vs €9,236). The patients' annual healthcare costs were substantially higher than controls for most types of healthcare across all age groups (Tables S3-S6). However, middle aged and elderly patients had substantially lower costs of nursing homes than controls in postintervention year 1 (€866 vs. €2,761). The costs of nursing homes remained substantially lower in elderly patients in postintervention year 2 and 3 (€1,763 (year 2) and €1,990 (year 3) vs. €2,761 for controls). In addition, costs of home care were lower for elderly patients than controls in the first year after the intervention (€1,199 vs. €1,330).

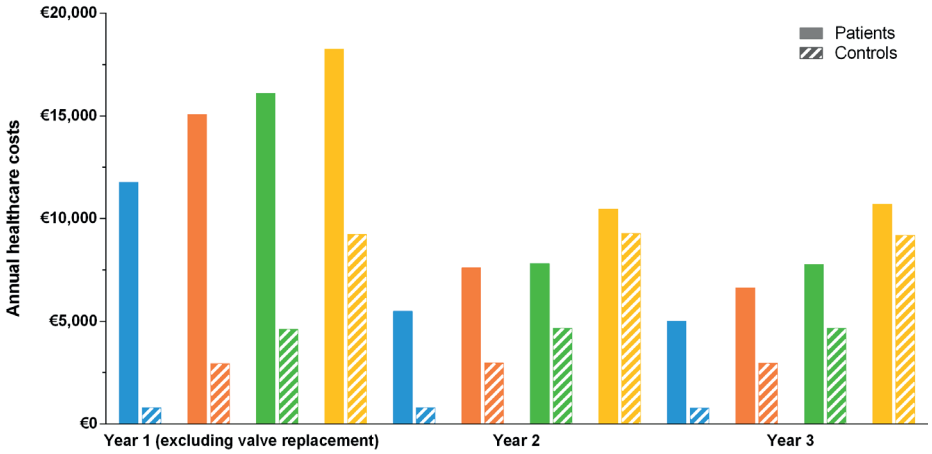
Healthcare costs – association analyses

Table 4 presents the results of the MGLMs of annual healthcare costs for children and adult SVR patients. Annual healthcare costs for adult SVR patients increased with older age at intervention (on average +€2,441 for elderly vs middle aged patients), comorbidities (on average +€6,543 for patients with chronic obstructive pulmonary disease, diabetes mellitus, kidney disease and/or heart failure vs patients without comorbidities), lower SES (on average +€1,160 for patients with lowest vs highest SES). Men had somewhat lower costs than women (€1,110 on average). If patients experience a complication, their annual healthcare costs increase on average with €623 after AF to €30,094 after re-intervention. If patients die, their costs in the year of death increase on average with €6,106. For children, costs were not associated with gender or SES. The results of the GLMs for intervention and complication costs are reported in Tables S7-8.

Table 3. Costs of initial heart valve intervention and complications

	Children (0-18 years)		Young adults (19-60 years)		Middle aged (61-70 years)		Elderly (>70 years)	
	n	Costs	n	Costs	n	Costs	n	Costs
Intervention (including ICU*)								
SVR (total)	399	21,941 (20,543-23,811)	3,172	25,050 (24,446-25,711)	4,727	25,502 (25,054-25,988)	9,387	25,740 (25,414-26,058)
Aortic	29	20,068 (18,843-21,279)	2,428	23,935 (23,350-24,592)	4,050	24,553 (24,131-25,004)	8,448	25,165 (24,845-25,482)
Pulmonary	328	21,800 (20,144-23,978)	114	19,442 (18,598-20,297)	2	14,483 (11,966-17,009)	2	23,702 (21,923-25,518)
Mitral	17	26,885 (19,920-35,138)	427	27,449 (25,691-29,491)	475	28,493 (26,779-30,386)	646	29,408 (27,634-31,510)
Tricuspid	23	22,409 (19,226-27,671)	64	33,306 (26,339-41,758)	32	26,858 (21,833-33,760)	35	23,611 (21,577-25,923)
Aortic + mitral	2	25,451 (20,148-30,753)	194	37,985 (32,581-44,947)	167	39,834 (34,892-45,874)	256	35,759 (33,074-38,668)
TVI (total)	0	-	29	33,385 (30,842-36,490)	64	32,440 (30,860-34,142)	744	32,209 (31,582-32,883)
Aortic	0	-	6	35,884 (30,552-43,785)	21	33,135 (29,843-36,786)	366	32,776 (31,812-33,842)
Mitral	0	-	2	33,838 (22,789-44,831)	1	36,661 (36,661-36,661)	0	-
Unknown	0	-	21	32,614 (30,134-36,300)	42	32,003 (30,193-33,909)	378	31,660 (30,915-32,563)
Complications (including ICU)								
AKI	2	6,007 (2,617-9,407)	36	9,061 (5,575-13,552)	81	8,021 (6,303-9,988)	169	9,533 (7,597-11,769)
AF	11	2,702 (717-5,789)	548	1,418 (1,295-1,543)	1,087	1,229 (1,147-1,313)	2,187	1,210 (1,119-1,321)
Stroke	1	1,418 (1,418-1,418)	257	3,264 (2,458-4,197)	403	2,627 (2,222-3,129)	1,115	3,017 (2,731-3,341)
TIA	0	-	104	1,213 (990-1,470)	220	1,311 (1,122-1,522)	387	1,267 (1,155-1,394)
Endocarditis	6	7,971 (3,764-13,057)	254	7,418 (6,449-8,401)	292	7,543 (6,689-8,380)	380	8,815 (7,960-9,722)
MI	0	-	49	6,248 (4,264-9,517)	83	5,421 (4,524-6,518)	203	5,094 (4,509-5,911)
PI	4	4,884 (2,175-6,621)	118	10,987 (10,403-11,525)	209	12,395 (10,875-15,179)	619	11,596 (11,348-11,853)
Re-intervention	22	20,057 (18,326-21,784)	70	25,328 (21,590-30,273)	72	21,340 (19,249-24,120)	135	25,622 (23,138-28,862)

Results presented in Euros as mean (95% confidence interval). SVR: surgical valve implantation. TVI: transcatheter valve implantation. ICU: intensive care unit. AKI: acute kidney injury. AF: atrial fibrillation. TIA: transient ischemic attack. MI: myocardial infarction. PI: pacemaker implantation. *ICU costs during first year minus ICU costs after complications. Only patients with ≥30 days follow-up or died ≤30 days included to ensure all ICU costs after intervention were considered.



	n	Costs in € (95% CI)	n	Costs in € (95% CI)	n	Costs in € (95% CI)
Children						
Patients	325	11,766 (10,560-12,784)	236	5,495 (4,108-7,207)	134	5,015 (3,434-6,810)
Controls	4,170	796 (739-861)	4,170	802 (741-869)	4,170	786 (713-871)
Young adults						
Patients	2,552	15,060 (14,617-15,549)	1,666	7,596 (6,809-8,447)	792	6,633 (5,587-7,751)
Controls	33,960	2,944 (2,870-3,021)	33,960	2,972 (2,892-3,054)	33,960	2,955 (2,873-3,043)
Middle aged						
Patients	3,773	16,104 (15,620-16,522)	2,331	7,823 (7,195-8,559)	1,137	7,764 (6,913-8,703)
Controls	50,440	4,612 (4,536-4,693)	50,440	4,679 (4,599-4,763)	50,440	4,681 (4,594-4,770)
Elderly						
Patients	7,619	18,255 (17,942-18,585)	4,544	10,478 (9,951-11,051)	2,217	10,701 (10,031-11,384)
Controls	100,355	9,236 (9,148-9,330)	100,355	9,273 (9,181-9,367)	100,355	9,200 (9,108-9,298)

Figure 2. Annual healthcare costs during the first three postintervention years of surgical valve replacement patients and controls divided by age group. CI: confidence interval

Table 4. Multilevel generalised linear model of total annual healthcare costs after SVR in postintervention years 1-4.

Total costs	Children (0-18 years, n=325)			Adults (>18 years, n=13,944)		
Parameter	**β**	**95% CI**	**P-value**	**β**	**95% CI**	**P-value**
Intercept	16,931	-36,190-70,051	0.533	11,338	9,906-12,770	<.0001
Time (compared to year 1 excluding intervention costs)						
Intervention period[1]	21,841	20,857-22,825	<.0001	25,492	25,248-25,736	<.0001
Year 2	-11,519	-67,302-44,264	0.686	-2,904	-3,779--2,030	<.0001
Year 3	-14,952	-67,272-37,368	0.576	-1,862	-3,421--302	0.019
Year 4	-6,170	-64,405-52,065	0.836	396	-1,627-2,420	0.701
Death				6,106	4,784-7,428	<.0001
Age (compared to elderly)						
Children (0-18 years)						
Young adults (19-60 years)				-1,179	-2,290--68	0.038
Middle aged (61-70 years)				-2,441	-3,359--1,524	<.0001
Male	1,133	-30,369-32,635	0.944	-1,110	-1,911--310	0.007
Co-morbidity (compared to no co-morbidity)						
COPD, DM, kidney disease and/or HF				6,543	5,328-7,757	<.0001
Hypertension				1,309	67-2,550	0.039
Other comorbidities				1,990	218-3,761	0.028
SES[2](compared to highest SES: 71-100)						
SES 0-20	8,553	-36,202-53,308	0.708	1,160	34-2,285	0.044
SES 21-40	2,878	-41,065-46,821	0.898	301	-823-1,426	0.599
SES 41-70	2,505	-37,038-42,048	0.901	887	-128-1,901	0.087
Complications						
AF				2,985	1,673-4,296	<.0001
AKI				19,639	16,611-22,667	<.0001
Stroke				7,755	6,181-9,329	<.0001
TIA				623	-2,157-3,403	0.661
Endocarditis				21,572	18,999-24,144	<.0001
MI				13,192	9,291-17,092	<.0001
PI				15,947	13,816-18,079	<.0001
Re-intervention				30,094	25,455-34,733	<.0001

SVR: surgical valve replacement. COPD: Chronic Obstructive Pulmonary Disease. DM: diabetes mellitus. HF: heart failure. SES: socioeconomic status. AKI: acute kidney injury. AF: atrial fibrillation. TIA: transient ischemic attack. MI: myocardial infarction. PI: pacemaker implantation.
N.B. 3,622 SVR and all TVI patients were excluded because follow-up < 1 year.
[1]Includes costs of heart valve implantation and ICU stay, but no other costs of the first postintervention year (these are included in the reference group of this variable) [2]Higher percentiles represent higher SES.

DISCUSSION

Using the comprehensive Vektis databases, we were able to estimate the real-world age group-specific incidence of heart valve implantations, subsequent survival and complications as well as the associated healthcare costs of all patients in the Netherlands who had undergone a heart valve implantation during our study period. Although the estimates are specific to the Dutch healthcare system, the results regarding differences between age groups, distribution of costs over types of healthcare and associations between patient and intervention characteristics and healthcare costs are also relevant for other countries. Our results can help raise awareness of the costs associated with heart valve implantations among clinicians and healthcare policy makers, which is important in the current era of limited healthcare budgets. However, we want to emphasise that considerations about costs should not play a role in the treatment decision for individual patients. Instead the results can be used as a benchmark in cost-effectiveness analyses for new technologies that will be introduced in clinical practice in the future, such as tissue-engineered heart valves.[5] This study has shown that Dutch health insurers spent over €120 million per year on procedure costs for heart valve implantations, of which 2% is spent on children, 17% on young adults, 26% on middle aged, and 56% on elderly patients. Although there were no substantial differences in procedure costs between age groups, the costs of SVR were generally higher in older patients, while costs of TVI were lower for older patients. There was no trend in complication costs in relation to age groups. In addition to procedure costs, patients had excess healthcare costs after the heart valve implantation compared to controls in almost all types of healthcare. These excess healthcare costs were especially high in the year of heart valve implantation; 41 (children), 14 (young adults), 9 (middle aged), and 5 (elderly) fold higher in patients than controls. In the subsequent postintervention years, however, the excess healthcare costs decreased. This decrease may be explained by survival of the fittest patients.

In contrast to other types of healthcare, the costs of nursing homes were substantially lower for elderly patients than for controls. This may be caused by selection bias of relatively healthy elderly patients for SVR. Patients living in nursing homes may be less likely to undergo heart valve implantation due to other factors influencing someone's health state, such as frailty or dementia. Since these factors could not be taken into account when defining the control sample, people living in nursing homes may be over-represented in the control group as compared with the patient group.

As expected, older age, female gender, comorbidities, low SES, and/or experiencing complications (including death) were associated with higher annual healthcare costs. It should be noted that the aim of this study was to describe and predict costs and that it does not make casual claims. Nevertheless, some explanations for the associations can be

considered. The association of lower SES and poor health has also been shown consistently in previous research.[10] The association of gender and costs, even after adjusting for comorbidities and complications, is in line with previous research that found that women have higher healthcare costs than men.[11] In cardiovascular diseases, this might be due to the different preoperative risks profiles of women compared to men[12, 13], which may be caused by delayed presentation or diagnosis of valve problems and/or later referral to cardiothoracic surgery of women.[12] If these different risk profiles result in slower or impaired recovery of women compared with men, this might result in more use of healthcare and thereby higher annual healthcare costs.

Strengths and limitations

An important strength of our study is the use of databases including the health insurance claims of 99% of Dutch residents. Therefore, almost all patients that have undergone heart valve implantations during our study period were included, and we presented outcomes in a diverse study population that reflects the range and distribution of patients in clinical practice instead of focusing on specific age or risk groups.[14] This resulted in comprehensive analyses of the real-world healthcare costs associated with heart valve implantations with high external validity and generalisability. Since healthcare decision makers need information about the cost-effectiveness in the real world, our results provide valuable input for the costs in cost-effectiveness analyses based on data generated in routine care instead of under experimental conditions.[14] Furthermore, this study provided an unique insight in the differences in incidence, health outcomes and associated healthcare costs of heart valve implantations of patients with all ages, divided over four informative age groups.

Our study also has some limitations. First, we could not separate our results for different types of valve prostheses (e.g. mechanical and biological prostheses). However, although the type of prosthesis has impact on survival and complication rates, we do not expect that the type of prosthesis has a large impact on healthcare costs. Furthermore, since the DRG code for TVI was only available from 2013, the follow-up was too short to estimate annual healthcare costs in postintervention years for these patients. Additionally, since complications were identified using DRG codes, we could only determine the incidence and costs of complications for which patients were treated in the hospital (including outpatient treatment). Furthermore, not all inhospital complications could be identified because for some complications the costs may be included in the DRG of the initial heart valve implantation instead of a separate DRG. In addition, the exact date of the heart valve implantation was unknown; instead, the opening date of the DRG in the financial administrative system was used as a proxy. It is possible that the heart valve implantation took place a few days/weeks before or after the opening date of the DRG. Furthermore, we could not calculate annual healthcare costs from the exact date of the intervention onwards but only from the quarter in which the intervention took place. Finally, the reported costs

are expenditures reimbursed by health insurers based on agreements between healthcare providers and insurers, not actual costs.

Conclusion

This study provided a comprehensive overview of age group-specific incidence of heart valve implantations, subsequent survival and complications as well as the associated healthcare costs of all patients who had undergone a heart valve implantation in the Netherlands. We have shown that after heart valve implantation, patients have substantially higher healthcare costs than controls. The costs are higher in patients with comorbidities and patients who have experienced a complication. The costs estimated in this study can be used as a benchmark for future innovative heart valve implantations, such as tissue-engineered heart valves.

Funding. This work was supported by the Netherlands Cardio Vascular Research Initiative: The Dutch Heart Foundation, Dutch Federation of University Medical Centers, the Netherlands Organization for Health Research and Development and the Royal Netherlands Academy of Sciences.

Conflicts of interest. None.

REFERENCES

1. Coffey, S., B.J. Cairns, and B. Iung, *The modern epidemiology of heart valve disease.* Heart, 2016. **102**(1): p. 75-85.
2. Nkomo, V.T., et al., *Burden of valvular heart diseases: a population-based study.* The Lancet, 2006. **368**(9540): p. 1005-1011.
3. Yacoub, M.H. and J.J.M. Takkenberg, *Will heart valve tissue engineering change the world?* Nat Clin Pract Cardiovasc Med, 2005. **2**(2): p. 60-61.
4. Vahanian, A., et al., *Guidelines on the management of valvular heart disease (version 2012) The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS).* European Heart Journal, 2012. **33**(19): p. 2451-2496.
5. Huygens, S.A., et al., *Conceptual model for early health technology assessment of current and novel heart valve interventions.* Open Heart, 2016. **3**(2): p. e000500.
6. Osnabrugge, R.L.J., et al., *Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients.* The Annals of thoracic surgery, 2012. **94**(6): p. 1954-1960.
7. Reynolds, M.R., et al., *Cost-effectiveness of transcatheter aortic valve replacement with a self-expanding prosthesis versus surgical aortic valve replacement.* Journal of the American College of Cardiology, 2016. **67**(1): p. 29-38.
8. Sociaal Cultureel Planbureau (SCP), *Statusscores 2009*. 2009.
9. Lamers, L.M. and R.C.J.A. van Vliet, *The Pharmacy-based Cost Group model: validating and adjusting the classification of medications for chronic conditions to the Dutch situation.* Health policy, 2004. **68**(1): p. 113-121.
10. Mackenbach, J.P., et al., *Socioeconomic inequalities in morbidity and mortality in western Europe.* The lancet, 1997. **349**(9066): p. 1655-1659.
11. Cylus, J., et al., *Pronounced gender and age differences are evident in personal health care spending per person.* Health Affairs, 2010: p. 10.1377/hlthaff. 2010.0216.
12. Ibrahim, M.F., et al., *Gender-related differences in morbidity and mortality during combined valve and coronary surgery.* The Journal of Thoracic and Cardiovascular Surgery, 2003. **126**(4): p. 959-964.
13. Mokhles, M.M., et al., *Male–female differences and survival in patients undergoing isolated mitral valve surgery: a nationwide cohort study in the Netherlands.* European Journal of Cardio-Thoracic Surgery, 2016. **50**(3): p. 482-487.
14. Garrison, L.P., et al., *Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report.* Value in Health, 2007. **10**(5): p. 326-335.

SUPPLEMENTARY MATERIAL

Strata used for comorbidities in generating the control group using stratified sampling methods

The strata used for comorbidities differed per age class because of differences in prevalence of comorbidities. In children, the prevalence of comorbidities was very low and therefore we did not stratify for comorbidities in this age group. In patients between 19 and 40 years old, hypertension was the only common co-morbidity and therefore we used two strata in these age classes: patients with and without hypertension. For each age class above 40 years old, we used four strata: (1) Patients with chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), kidney disease and/or heart failure (HF) (44.9%); (2) Patients with hypertension and without the comorbidities defined in group 1 (31.1%); (3) Patients with other comorbidities than defined in group 1 and 2 (7.0%); and (4) Patients without comorbidities (12.2%). The specific comorbidities were chosen because they were the most frequently occurring comorbidities in heart valve disease patients.

Table S1. DRG codes of heart valve implantations

Diagnosis code	Description diagnosis	Treatment code	Description treatment	Children	Young adults	Middle aged	Elderly	Unknown
2770	Aortic root + CABG + MPL/ MVR	110027700120	First surgery with implantation		9	9	9	
2770	Aortic root + CABG + MPL/ MVR	979001058	Surgery ascending aorta with two or more valves – with hospital stay		4	7	2	
2770	Aortic root + CABG + MPL/ MVR	979001057	Surgery ascending aorta with two or more valves – without hospital stay				1	
2770	Aortic root + CABG + MPL/ MVR	110027700220	Reoperation with implantation		4	1	1	
2660	Aortic root + MVR/MPL	110026600120	First surgery with implantation		9	7	4	
2660	Aortic root + MVR/MPL	110026600220	Reoperation with implantation		4	5	2	
2660	Aortic root + MVR/MPL	979001057	Surgery ascending aorta with two or more valves – without hospital stay		1	1	1	
2660	Aortic root + MVR/MPL	979001058	Surgery ascending aorta with two or more valves – with hospital stay		10	4	1	
2660	Aortic root + MVR/MPL	110026600420	Combined heart/artery surgery with implantation			2		
2325	Aortic valve replacement (AVR)	110023250120	First surgery with implantation	6	636	964	2135	3
2325	Aortic valve replacement (AVR)	979001038	Isolated valve surgery – with hospital stay	2	340	533	1009	4
2325	Aortic valve replacement (AVR)	979001193	Valve surgery - 1 cost unit	6	348	519	881	1
2325	Aortic valve replacement (AVR)	979001188	Transcatheter valve implantation - Non-coronary intervention class 3 – with hospital stay		6	22	325	
2325	Aortic valve replacement (AVR)	110023250220	Reoperation with implantation	3	72	86	182	
2325	Aortic valve replacement (AVR)	979001037	Isolated valve surgery – without hospital stay	1	1	9	73	
2325	Aortic valve replacement (AVR)	979001189	Transcatheter valve implantation - Non-coronary intervention class 3 - without hospital stay			3	68	
2325	Aortic valve replacement (AVR)	979001192	Valve surgery - 2 cost units				25	
2325	Aortic valve replacement (AVR)	979001028	Two/Multiple valve surgery – with hospital stay	1	5	13	20	
2325	Aortic valve replacement (AVR)	110023250320	Combined heart/lung surgery with implantation		1	3	5	

Table S1. Continued

Diagnosis code	Description diagnosis	Treatment code	Description treatment	Children	Young adults	Middle aged	Elderly	Unknown
2325	Aortic valve replacement (AVR)	979001027	Two/Multiple valve surgery – without hospital stay	1		1	3	
2325	Aortic valve replacement (AVR)	979001191	Valve surgery - 3 cost units				2	
2325	Aortic valve replacement (AVR)	979001190	Valve surgery - at least 4 cost units			1		
2325	Aortic valve replacement (AVR)	979001192	Valve surgery - 2 cost units		18	16		
2325	Aortic valve replacement (AVR)	110023250420	Combined heart/artery surgery with implantation		1	2		
2680	AVR + Ascending aorta	110026800120	First surgery with implantation		88	93	61	
2680	AVR + Ascending aorta	979001068	Surgery ascending aorta with a valve – with hospital stay		68	55	44	
2680	AVR + Ascending aorta	110026800220	Reoperation with implantation		12	8	7	1
2680	AVR + Ascending aorta	110026800110	First surgery		3	4	2	
2680	AVR + Ascending aorta	979001067	Surgery ascending aorta with a valve – without hospital stay		2			
2680	AVR + Ascending aorta	110026800320	Combined heart/lung surgery with implantation			1		
2655	AVR + CABG + HOCM	110026550120	First surgery with implantation		1	2	18	
2655	AVR + CABG + HOCM	979001046	Isolated valve surgery with CABG – with hospital stay				4	
2655	AVR + CABG + HOCM	979001191	Valve surgery - 3 cost units				3	
2655	AVR + CABG + HOCM	979001036	Two/Multiple valve surgery with CABG – with hospital stay				1	
2655	AVR + CABG + HOCM	979001192	Valve surgery - 2 cost units				1	
2655	AVR + CABG + HOCM	110026550110	First surgery		1		1	
2580	AVR + HOCM	110025800120	First surgery with implantation		4	6	7	
2580	AVR + HOCM	979001038	Isolated valve surgery – with hospital stay			6	6	
2580	AVR + HOCM	979001193	Valve surgery - 1 cost unit				4	
2580	AVR + HOCM	979001192	Valve surgery - 2 cost units		1		3	
2580	AVR + HOCM	979001191	Valve surgery - 3 cost units				2	
2580	AVR + HOCM	979001037	Isolated valve surgery – without hospital stay				1	
2580	AVR + HOCM	110025800220	Reoperation with implantation				1	
2580	AVR + HOCM	979001038	Isolated valve surgery – with hospital stay		2			
2580	AVR + HOCM	110025800110	First surgery		2			

Table S1. Continued

Diagnosis code	Description diagnosis	Treatment code	Description treatment	Children	Young adults	Middle aged	Elderly	Unknown
2575	AVR + MPL	110025750120	First surgery with implantation		49	58	109	
2575	AVR + MPL	979001192	Valve surgery - 2 cost units	1	26	33	71	
2575	AVR + MPL	979001028	Two/Multiple valve surgery – with hospital stay		17	31	47	
2575	AVR + MPL	110025750220	Reoperation with implantation		1	7	10	
2575	AVR + MPL	979001038	Isolated valve surgery – with hospital stay		1		5	
2575	AVR + MPL	979001190	Valve surgery - at least 4 cost units		1		3	
2575	AVR + MPL	979001193	Valve surgery - 1 cost unit		2		3	
2575	AVR + MPL	110025750110	First surgery		2	5	3	
2575	AVR + MPL	979001027	Two/Multiple valve surgery – without hospital stay		1		2	
2575	AVR + MPL	979001191	Valve surgery - 3 cost units		6	1		
2420	AVR + MVR	110024200120	First surgery with implantation		30	35	39	1
2420	AVR + MVR	979001028	Two/Multiple valve surgery – with hospital stay		16	10	17	
2420	AVR + MVR	979001192	Valve surgery - 2 cost units	1	10	15	15	
2420	AVR + MVR	110024200220	Reoperation with implantation		8	2	6	
2420	AVR + MVR	110024200110	First surgery			1	3	
2420	AVR + MVR	979001027	Two/Multiple valve surgery – without hospital stay		2		2	
2420	AVR + MVR	979001038	Isolated valve surgery – with hospital stay		1	1	2	
2420	AVR + MVR	979001193	Valve surgery - 1 cost unit			1		
2565	AVR + MVR + TPL	110025650120	First surgery with implantation		5	2	13	
2565	AVR + MVR + TPL	979001028	Two/Multiple valve surgery – with hospital stay		2	2	10	
2565	AVR + MVR + TPL	979001191	Valve surgery - 3 cost units		8	5	10	
2565	AVR + MVR + TPL	110025650110	First surgery			1	3	
2565	AVR + MVR + TPL	110025650220	Reoperation with implantation			1	2	
2695	AVR + MVR +/- TPL	110026950120	First surgery with implantation		15	16	21	
2695	AVR + MVR +/- TPL	979001028	Two/Multiple valve surgery – with hospital stay		11	11	20	
2695	AVR + MVR +/- TPL	979001191	Valve surgery - 3 cost units		2	9	13	
2695	AVR + MVR +/- TPL	979001192	Valve surgery - 2 cost units		6	6	9	
2695	AVR + MVR +/- TPL	110026950220	Reoperation with implantation		3	1	9	
2695	AVR + MVR +/- TPL	979001190	Valve surgery - at least 4 cost units		1	3	3	

Table S1. Continued

Diagnosis code	Description diagnosis	Treatment code	Description treatment	Children	Young adults	Middle aged	Elderly	Unknown
2695	AVR + MVR +/- TPL	979001193	Valve surgery - 1 cost unit				2	
2695	AVR + MVR +/- TPL	979001027	Two/Multiple valve surgery – without hospital stay		1	1	1	
2695	AVR + MVR +/- TPL	110026950210	Reoperation			2	1	
2695	AVR + MVR +/- TPL	979001038	Isolated valve surgery – with hospital stay		1			
2695	AVR + MVR +/- TPL	110026950110	First surgery		1	1		
2790	AVR+ascending aorta+MPL+/- TPL	110027900120	First surgery with implantation		9	12	19	
2790	AVR+ascending aorta+MPL+/- TPL	979001058	Surgery ascending aorta with two or more valves – with hospital stay		16	12	13	
2790	AVR+ascending aorta+MPL+/- TPL	110027900220	Reoperation with implantation			5	3	
2790	AVR+ascending aorta+MPL+/- TPL	110027900420	Combined heart/artery surgery with implantation				1	
2790	AVR+ascending aorta+MPL+/- TPL	979001057	Surgery ascending aorta with two or more valves – without hospital stay			1		
2790	AVR+ascending aorta+MPL+/- TPL	110027900210	Reoperation			1		
2790	AVR+ascending aorta+MPL+/- TPL	110027900220	Reoperation with implantation		2			
2545	Bentall	110025450120	First surgery with implantation	2	163	79	40	
2545	Bentall	979001068	Surgery ascending aorta with a valve – with hospital stay	1	86	54	30	
2545	Bentall	110025450220	Reoperation with implantation	3	38	15	15	
2545	Bentall	110025450110	First surgery	1	6	6	5	
2545	Bentall	979001067	Surgery ascending aorta with a valve – without hospital stay	1	3	4	3	
2545	Bentall	110025450420	Combined heart/artery surgery with implantation		6	2	1	
2545	Bentall	110025450210	Reoperation		1	1		
2545	Bentall	110025450410	Combined heart/artery surgery			1		
2425	CABG (1 art) + AVR	110024250120	First surgery with implantation		131	483	1304	1
2425	CABG (1 art) + AVR	979001046	Isolated valve surgery with CABG – with hospital stay		46	225	656	
2425	CABG (1 art) + AVR	979001192	Valve surgery - 2 cost units		57	193	530	1
2425	CABG (1 art) + AVR	979001191	Valve surgery - 3 cost units		10	35	75	
2425	CABG (1 art) + AVR	110024250220	Reoperation with implantation		8	20	42	

Table S1. Continued

Diagnosis code	Description diagnosis	Treatment code	Description treatment	Children	Young adults	Middle aged	Elderly	Unknown
2425	CABG (1 art) + AVR	979001045	Isolated valve surgery with CABG – without hospital stay			4	19	
2425	CABG (1 art) + AVR	979001193	Valve surgery - 1 cost unit		3	10	17	
2425	CABG (1 art) + AVR	979001036	Two/Multiple valve surgery with CABG – with hospital stay		1	2	7	
2425	CABG (1 art) + AVR	110024250320	Combined heart/lung surgery with implantation				4	
2425	CABG (1 art) + AVR	979001190	Valve surgery - at least 4 cost units		1		3	
2425	CABG (1 art) + AVR	979001188	Transcatheter valve implantation - Non-coronary intervention class 3 - with hospital stay				2	
2425	CABG (1 art) + AVR	110024250420	Combined heart/artery surgery with implantation				2	
2415	CABG (1 art) + MVR	110024150120	First surgery with implantation		27	57	93	
2415	CABG (1 art) + MVR	979001046	Isolated valve surgery with CABG – with hospital stay		12	32	72	
2415	CABG (1 art) + MVR	979001192	Valve surgery - 2 cost units		10	15	28	
2415	CABG (1 art) + MVR	110024150110	First surgery		3	3	7	
2415	CABG (1 art) + MVR	110024150220	Reoperation with implantation		1	2	7	
2415	CABG (1 art) + MVR	979001045	Isolated valve surgery with CABG – without hospital stay		1	3	3	
2415	CABG (1 art) + MVR	979001036	Two/Multiple valve surgery with CABG – with hospital stay		1	2	2	
2415	CABG (1 art) + MVR	979001190	Valve surgery - at least 4 cost units			1	2	
2415	CABG (1 art) + MVR	979001193	Valve surgery - 1 cost unit				2	
2415	CABG (1 art) + MVR	110024150210	Reoperation			1	2	
2415	CABG (1 art) + MVR	110024150420	Combined heart/artery surgery with implantation				2	
2415	CABG (1 art) + MVR	979001191	Valve surgery - 3 cost units		2	4	1	
2415	CABG (1 art) + MVR	110024150310	Combined heart/lung surgery				1	
2560	CABG (1art) + AVR + MVR	110025600120	First surgery with implantation		5	16	26	
2560	CABG (1art) + AVR + MVR	979001036	Two/Multiple valve surgery with CABG – with hospital stay			6	14	
2560	CABG (1art) + AVR + MVR	979001191	Valve surgery - 3 cost units		3	5	4	
2560	CABG (1art) + AVR + MVR	979001035	Two/Multiple valve surgery with CABG – without hospital stay				2	
2560	CABG (1art) + AVR + MVR	979001190	Valve surgery - at least 4 cost units		1		2	

Table S1. Continued

Diagnosis code	Description diagnosis	Treatment code	Description treatment	Children	Young adults	Middle aged	Elderly	Unknown
2560	CABG (1art) + AVR + MVR	979001192	Valve surgery - 2 cost units			2	2	
2560	CABG (1art) + AVR + MVR	979001046	Isolated valve surgery with CABG – with hospital stay			1	1	
2560	CABG (1art) + AVR + MVR	110025600110	First surgery				1	
2560	CABG (1art) + AVR + MVR	110025600220	Reoperation with implantation				1	
2570	CABG (2 art) + AVR	110025700120	First surgery with implantation		39	102	234	1
2570	CABG (2 art) + AVR	979001046	Isolated valve surgery with CABG – with hospital stay		17	61	105	
2570	CABG (2 art) + AVR	979001192	Valve surgery - 2 cost units		12	39	79	
2570	CABG (2 art) + AVR	979001191	Valve surgery - 3 cost units		3	2	8	
2570	CABG (2 art) + AVR	110025700110	First surgery		3	4	7	
2570	CABG (2 art) + AVR	110025700220	Reoperation with implantation			1	6	
2570	CABG (2 art) + AVR	979001036	Two/Multiple valve surgery with CABG – with hospital stay			1	3	
2570	CABG (2 art) + AVR	979001190	Valve surgery - at least 4 cost units			1	3	
2570	CABG (2 art) + AVR	979001045	Isolated valve surgery with CABG – without hospital stay				2	
2570	CABG (2 art) + AVR	979001193	Valve surgery - 1 cost unit			1	2	
2570	CABG (2 art) + AVR	110025700210	Reoperation			2		
2570	CABG (2 art) + AVR	110025700420	Combined heart/artery surgery with implantation			1		
2555	CABG (2 art) + MVR	110025550120	First surgery with implantation		5	9	12	
2555	CABG (2 art) + MVR	979001046	Isolated valve surgery with CABG – with hospital stay		2	9	9	
2555	CABG (2 art) + MVR	979001192	Valve surgery - 2 cost units		2	6	2	
2555	CABG (2 art) + MVR	110025550220	Reoperation with implantation				2	
2555	CABG (2 art) + MVR	979001045	Isolated valve surgery with CABG – without hospital stay		1	1	1	
2555	CABG (2 art) + MVR	979001190	Valve surgery - at least 4 cost units			1		
2555	CABG (2 art) + MVR	979001191	Valve surgery - 3 cost units			1		
502	Congenital heart defect	979001188	Transcatheter valve implantation - Non-coronary intervention class 3 - with hospital stay		15		1	
501	Heart defect	979001188	Transcatheter valve implantation - Non-coronary intervention class 3 - with hospital stay		10	42	407	

Table S1. Continued

Diagnosis code	Description diagnosis	Treatment code	Description treatment	Children	Young adults	Middle aged	Elderly	Unknown
501	Heart defect	979001189	Transcatheter valve implantation - Non-coronary intervention class 3 - without hospital stay			2	6	
2475	Left ventricle repair+AVR/ MVR	110024750120	First surgery with implantation		3	4	3	
2475	Left ventricle repair+AVR/ MVR	979001192	Valve surgery - 2 cost units		1	4	1	
2475	Left ventricle repair+AVR/ MVR	110024750220	Reoperation with implantation		2	3	1	
2475	Left ventricle repair+AVR/ MVR	979001028	Two/Multiple valve surgery – with hospital stay		1	4		
2475	Left ventricle repair+AVR/ MVR	979001038	Isolated valve surgery – with hospital stay		2	1		
2475	Left ventricle repair+AVR/ MVR	979001190	Valve surgery - at least 4 cost units		1			
2475	Left ventricle repair+AVR/ MVR	979001191	Valve surgery - 3 cost units			1		
2475	Left ventricle repair+AVR/ MVR	979001193	Valve surgery - 1 cost unit	1				
2785	Maze+CABG of AVR+MPL +/- TPL	110027850120	First surgery with implantation		24	98	235	
2785	Maze+CABG of AVR+MPL +/- TPL	979001044	Surgical treatment atrium fibrillation/with multiple valves– with hospital stay		15	55	98	
2785	Maze+CABG of AVR+MPL +/- TPL	979001191	Valve surgery - 3 cost units		11	22	40	
2785	Maze+CABG of AVR+MPL +/- TPL	979001192	Valve surgery - 2 cost units		2	11	17	
2785	Maze+CABG of AVR+MPL +/- TPL	979001190	Valve surgery - at least 4 cost units		5	13	15	
2785	Maze+CABG of AVR+MPL +/- TPL	110027850110	First surgery		1	5	6	
2785	Maze+CABG of AVR+MPL +/- TPL	110027850220	Reoperation with implantation			7	6	
2785	Maze+CABG of AVR+MPL +/- TPL	979001043	Surgical treatment atrium fibrillation/with multiple valves– without hospital stay			1	1	
2335	Mitral valve replacement (MVR)	110023350120	First surgery with implantation	3	97	72	100	
2335	Mitral valve replacement (MVR)	979001038	Isolated valve surgery – with hospital stay	2	48	53	56	

Table S1. Continued

Diagnosis code	Description diagnosis	Treatment code	Description treatment	Children	Young adults	Middle aged	Elderly	Unknown
2335	Mitral valve replacement (MVR)	979001193	Valve surgery - 1 cost unit	4	48	42	42	
2335	Mitral valve replacement (MVR)	110023350220	Reoperation with implantation	7	37	30	35	
2335	Mitral valve replacement (MVR)	979001192	Valve surgery - 2 cost units	1	16	19	29	
2335	Mitral valve replacement (MVR)	979001037	Isolated valve surgery – without hospital stay	1	4	5	7	
2335	Mitral valve replacement (MVR)	110023350110	First surgery		3	8	5	
2335	Mitral valve replacement (MVR)	979001028	Two/Multiple valve surgery – with hospital stay	1	7	7	2	
2335	Mitral valve replacement (MVR)	979001191	Valve surgery - 3 cost units				1	
2335	Mitral valve replacement (MVR)	110023350210	Reoperation		1	1	1	
2335	Mitral valve replacement (MVR)	979001188	Transcatheter valve implantation - Non-coronary intervention class 3 - with hospital stay		1	1		
2335	Mitral valve replacement (MVR)	979001189	Transcatheter valve implantation - Non-coronary intervention class 3 - without hospital stay		1			
2335	Mitral valve replacement (MVR)	110023350320	Combined heart/lung surgery with implantation					1
2645	MPL + AVR + CABG	110026450120	First surgery with implantation		16	39	83	
2645	MPL + AVR + CABG	979001036	Two/Multiple valve surgery with CABG – with hospital stay		4	18	35	
2645	MPL + AVR + CABG	979001191	Valve surgery - 3 cost units		4	22	25	
2645	MPL + AVR + CABG	979001190	Valve surgery - At least 4 cost units		2	3	9	
2645	MPL + AVR + CABG	979001046	Isolated valve surgery with CABG – with hospital stay		1	2	5	
2645	MPL + AVR + CABG	110026450220	Reoperation with implantation		1		4	
2645	MPL + AVR + CABG	110026450110	First surgery				3	
2645	MPL + AVR + CABG	979001035	Two/Multiple valve surgery with CABG – without hospital stay				1	
2645	MPL + AVR + CABG	979001045	Isolated valve surgery with CABG – without hospital stay				1	
2645	MPL + AVR + CABG	979001192	Valve surgery - 2 cost units		1		1	

Table S1. Continued

Diagnosis code	Description diagnosis	Treatment code	Description treatment	Children	Young adults	Middle aged	Elderly	Unknown
2645	MPL + AVR + CABG	110026450210	Reoperation				1	
2465	MVR + TPL	110024650120	First surgery with implantation		24	20	44	
2465	MVR + TPL	979001192	Valve surgery - 2 cost units		13	13	25	
2465	MVR + TPL	979001028	Two/Multiple valve surgery – with hospital stay		10	15	21	
2465	MVR + TPL	110024650220	Reoperation with implantation		11	7	10	
2465	MVR + TPL	979001191	Valve surgery - 3 cost units		2	5	3	
2465	MVR + TPL	979001027	Two/Multiple valve surgery – without hospital stay		1	1	2	
2465	MVR + TPL	979001038	Isolated valve surgery – with hospital stay		1			
2465	MVR + TPL	979001190	Valve surgery - at least 4 cost units			1		
2465	MVR + TPL	110024650110	First surgery			2		
2340	Pulmonary valve repair / replacement	979001037	Isolated valve surgery – without hospital stay	8			1	
2340	Pulmonary valve repair / replacement	979001038	Isolated valve surgery – with hospital stay	14	21		1	
2340	Pulmonary valve repair / replacement	979001027	Two/Multiple valve surgery – without hospital stay	1				
2340	Pulmonary valve repair / replacement	979001028	Two/Multiple valve surgery – with hospital stay	8	3			
2340	Pulmonary valve repair / replacement	979001192	Valve surgery - 2 cost units	3	2			
2340	Pulmonary valve repair / replacement	979001193	Valve surgery - 1 cost unit	31	20			
2340	Pulmonary valve repair / replacement	110023400110	First surgery	10				
2340	Pulmonary valve repair / replacement	110023400120	First surgery with implantation	16	15			
2340	Pulmonary valve repair / replacement	110023400210	Reoperation	12	1			
2340	Pulmonary valve repair / replacement	110023400220	Reoperation with implantation	48	47	2		
2435	Tetralogy of Fallot	979001009	Congenital heart surgery with ECC (complex) – without hospital stay	16				
2435	Tetralogy of Fallot	979001010	Congenital heart surgery with ECC (complex) – with hospital stay	23	1			
2435	Tetralogy of Fallot	979001210	Congenital heart surgery with ECC (complex) – without hospital stay	20	1			

Table S1. Continued

Diagnosis code	Description diagnosis	Treatment code	Description treatment	Children	Young adults	Middle aged	Elderly	Unknown
2435	Tetralogy of Fallot	979001211	Congenital heart surgery with ECC (complex) – with hospital stay	17				
2435	Tetralogy of Fallot	110024350110	First surgery	68	1			
2435	Tetralogy of Fallot	110024350120	First surgery with implantation	27				
2435	Tetralogy of Fallot	110024350210	Reoperation	9				
2435	Tetralogy of Fallot	110024350220	Reoperation with implantation	7	3			
2410	Tricuspid valve repair / replacement	110024100120	First surgery with implantation	7	18	13	12	
2410	Tricuspid valve repair / replacement	110024100220	Reoperation with implantation	2	13	6	10	
2410	Tricuspid valve repair / replacement	979001193	Valve surgery - 1 cost unit	2	13	9	5	
2410	Tricuspid valve repair / replacement	979001038	Isolated valve surgery – with hospital stay		10	3	4	
2410	Tricuspid valve repair / replacement	110024100110	First surgery	6	4		4	
2410	Tricuspid valve repair / replacement	979001028	Two/Multiple valve surgery – with hospital stay	3	1		1	
2410	Tricuspid valve repair / replacement	979001027	Two/Multiple valve surgery – without hospital stay	1				
2410	Tricuspid valve repair / replacement	979001037	Isolated valve surgery – without hospital stay	1				
2410	Tricuspid valve repair / replacement	979001190	Valve surgery - at least 4 cost units			1		
2410	Tricuspid valve repair / replacement	979001192	Valve surgery - 2 cost units		4	2		
2410	Tricuspid valve repair / replacement	110024100210	Reoperation	1	2			

CABG: coronary artery bypass grafting. AVR: aortic valve replacement. MVR: mitral valve replacement. MPL: mitral valve repair. TPL: tricuspid valve repair. HOCM: Hypertrophic Obstructive Cardiomyopathy. ECC: Extracorporeal Circulation.

Table S2. DRG codes of complications after heart valve implantations

					SVR				TVI	
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
Acute kidney injury										
322	Acute kidney insufficiency with dialysis	**140301009**	Haemodialysis in hospital - Acute dialysis - Not clinical - Dialysis 1-3 - Urogenital kidney insufficiency		9	18	29			7
322	Acute kidney insufficiency with dialysis	**140301010**	Haemodialysis in hospital - Acute dialysis - Clinical - Dialysis 1-3 - Urogenital kidney insufficiency		2	3	3			
322	Acute kidney insufficiency with dialysis	**140301025**	Haemodialysis in hospital - Acute dialysis - Not clinical - Dialysis 4-5 - Urogenital kidney insufficiency		6	3	20			2
322	Acute kidney insufficiency with dialysis	**140301026**	Haemodialysis in hospital - Acute dialysis - Clinical - Dialysis 4-5 - Urogenital kidney insufficiency		2	2				
322	Acute kidney insufficiency with dialysis	**140301045**	Haemodialysis in hospital - Acute dialysis - Not clinical - Dialysis >=6 - Urogenital kidney insufficiency		6	21	34			
322	Acute kidney insufficiency with dialysis	**140301047**	Haemodialysis in hospital - Acute dialysis - Clinical - Dialysis >=6 - Urogenital kidney insufficiency		1	4	5			
322	Acute kidney insufficiency with dialysis	**110003221103**	Clinical tests/treatment		6	9	30			
323	Acute kidney insufficiency without dialysis	**140301028**	Acute kidney insufficiency without dialysis - Clinical short		2	8	8			
323	Acute kidney insufficiency without dialysis	**140301049**	Acute kidney insufficiency without dialysis - Clinical long			1				
323	Acute kidney insufficiency without dialysis	**140301050**	Acute kidney insufficiency without dialysis - Clinical average			6	16			1
323	Acute kidney insufficiency without dialysis	**110003231103**	Clinical tests/treatment		2	6	15			
4005	Kidney insufficiency, acute	**990016040**	Clinical average	1						
4005	Kidney insufficiency, acute	**990016042**	Haemodialysis in hospital | Not clinical | Dialysis 1-3	1						

Table S2. Continued

					SVR			TVI		
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
Atrial fibrillation										
401	Atrium fibrillation / flutter	**99899064**	Supraventricular arrhythmias - day/clinical cumulative short	1	201	385	583			15
401	Atrium fibrillation / flutter	**99899063**	Supraventricular arrhythmias - Average ambulant	2	97	220	517	1		16
401	Atrium fibrillation / flutter	**99899072**	Supraventricular arrhythmias - Mild ambulant		57	167	384			6
401	Atrium fibrillation / flutter	**110004010103**	Regular treatment/no treatment with clinical periods		95	132	241			
401	Atrium fibrillation / flutter	**110004010101**	Regular treatment/no treatment outpatient		43	65	204			
401	Atrium fibrillation / flutter	**110004010102**	Regular treatment/no treatment with day admission(s)		28	81	138			
401	Atrium fibrillation / flutter	**99899074**	Supraventricular arrhythmias - day/clinical cumulative average		11	22	67			1
401	Atrium fibrillation / flutter	**979001102**	Catheter ablation class 2 - with hospital stay		2		3			
401	Atrium fibrillation / flutter	**979001237**	Catheter ablation class 2 - with hospital stay		2	3	2			1
401	Atrium fibrillation / flutter	**979001239**	Catheter ablation class 1 - with hospital stay				2			
401	Atrium fibrillation / flutter	**979001110**	Catheter ablation class 1 - with hospital stay			1	1			
401	Atrium fibrillation / flutter	**110004010313**	Catheter ablation class1 with clinical episodes		1		1			
401	Atrium fibrillation / flutter	**99899073**	Supraventricular arrhythmias - day/clinical cumulative long				1			
401	Atrium fibrillation / flutter	**979001238**	Catheter ablation class 2 - without hospital stay				1			
401	Atrium fibrillation / flutter	**979001233**	Catheter ablation class 4 - with hospital stay		4	2				
401	Atrium fibrillation / flutter	**110004010343**	Catheter ablation class4 with clinical episodes			2				

Table S2. Continued

					SVR				TVI	
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
401	Atrium fibrillation / flutter	**110004010323**	Catheter ablation class2 with clinical episodes		4	1				
401	Atrium fibrillation / flutter	**979001087**	Catheter ablation class 4 - with hospital stay		1	1				
401	Atrium fibrillation / flutter	**979001101**	Catheter ablation class 2 - without hospital stay		1	1				
401	Atrium fibrillation / flutter	**979001234**	Catheter ablation class 4 - without hospital stay			1				
2525	Maze procedure	**979001069**	Surgical treatment atrium fibrillation - without hospital stay				2			
2525	Maze procedure	**979001070**	Surgical treatment atrium fibrillation - with hospital stay			1				
2675	Maze + MVP/MPL +/- TPL	**110026750220**	Reoperation with implantation			1				
2785	Maze+CABG of AVR+MPL +/- TPL	**979001070**	Surgical treatment atrium fibrillation - with hospital stay			1	1			
3410	Arrhythmias	**990016087**	Other cardiovascular diagnoses | Clinical average	1						
3410	Arrhythmias	**990016102**	Other cardiovascular diagnoses | Mild ambulant	1						
3410	Arrhythmias	**990016103**	Other cardiovascular diagnoses | Other cardiologic activities	1						
3410	Arrhythmias	**990016114**	Other cardiovascular diagnoses | Clinical short | With other cardiologic activities	1						
3410	Arrhythmias	**990516028**	Other cardiologic diagnoses | Clinical short | Without other cardiologic activities	1						
3410	Arrhythmias	**990516035**	Other cardiologic diagnoses | Mild ambulant	1						
3410	Arrhythmias	**990516036**	Other cardiologic diagnoses | Ambulant average / Day =1 | Without other cardiologic activities	1						
3410	Arrhythmias	**990516039**	Other cardiologic diagnoses | Clinical average | With other cardiologic activities	1						

Table S2. Continued

					SVR			TVI		
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
Stroke										
1101	Subarachnoid haemorrhage	**99999003**	Subarachnoid haemorrhage - Clinical short				4			
1101	Subarachnoid haemorrhage	**99999010**	Subarachnoid haemorrhage - Clinical average			1				
1101	Subarachnoid haemorrhage	**99999040**	Subarachnoid haemorrhage - Clinical average - without guidance with neurological intervention				1			
1101	Subarachnoid haemorrhage	**99999042**	Subarachnoid haemorrhage - Clinical long - without guidance with neurological intervention				1			
1101	Subarachnoid haemorrhage	**110011010111**	Regular treatment outpatient		1	1	1			
1101	Subarachnoid haemorrhage	**110011010113**	Regular treatment with clinical episodes			1				
1102	Intracerebral haemorrhage	**99999008**	Intracerebral- / intracranial haemorrhage-Clinical short		2	3	21			
1102	Intracerebral haemorrhage	**99999012**	Intracerebral- / intracranial haemorrhage-Clinical long		1					
1102	Intracerebral haemorrhage	**99999013**	Intracerebral- / intracranial haemorrhage-Clinical average			4	6			
1102	Intracerebral haemorrhage	**99999045**	Intracerebral- / intracranial haemorrhage-Clinical average - without guidance with neurological intervention		5	2	6			1
1102	Intracerebral haemorrhage	**110011020111**	Regular treatment outpatient		4	1	5			
1102	Intracerebral haemorrhage	**110011020113**	Regular treatment with Clinical episodes		6	6	20			
1103	Intracranial haemorrhage (sub-/epidural)	**99999008**	Intracerebral- / intracranial haemorrhage-Clinical short		3	2	5			
1103	Intracranial haemorrhage (sub-/epidural)	**99999013**	Intracerebral- / intracranial haemorrhage-Clinical average				8			
1103	Intracranial haemorrhage (sub-/epidural)	**99999045**	Intracerebral- / intracranial haemorrhage-Clinical average - without guidance with neurological intervention		1		9			1

Table S2. Continued

					SVR				TVI	
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
1103	Intracranial haemorrhage (sub-/epidural)	**99999047**	Intracerebral- / intracranial haemorrhage-Clinical long - without guidance with neurological intervention				1			
1103	Intracranial haemorrhage (sub-/epidural)	**110011030111**	Regular treatment outpatient		3	2	4			
1103	Intracranial haemorrhage (sub-/epidural)	**110011030113**	Regular treatment with clinical episodes		4	3	9			
1103	Intracranial haemorrhage (sub-/epidural)	**110011030133**	Post-operative neurosurgical guidance patient with clinical episodes		1					
1111	Non-haemorrhagic stroke	**99999006**	CVA non-haemorrhagic and TIA - Day - Without clinical neurophysiology		1	1	11			
1111	Non-haemorrhagic stroke	**99999007**	CVA non-haemorrhagic and TIA - Day - With clinical neurophysiology		2	4	9			1
1111	Non-haemorrhagic stroke	**99999011**	CVA non-haemorrhagic and TIA - clinical neurophysiology severe		2	1	1			
1111	Non-haemorrhagic stroke	**99999016**	CVA non-haemorrhagic and TIA - clinical neurophysiology mild		13	33	68			1
1111	Non-haemorrhagic stroke	**99999017**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical short - Without clinical neurophysiology		8	15	36			1
1111	Non-haemorrhagic stroke	**99999018**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical short - With clinical neurophysiology		9	18	46			1
1111	Non-haemorrhagic stroke	**99999019**	CVA non-haemorrhagic/TIA/other cerebral disorders - Thrombolytic - Clinical short - Without clinical neurophysiology		1	1	4			
1111	Non-haemorrhagic stroke	**99999020**	CVA non-haemorrhagic/TIA/other cerebral disorders - Thrombolytic therapy - Clinical short - With clinical neurophysiology		1	1	2			2
1111	Non-haemorrhagic stroke	**99999025**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical long - With clinical neurophysiology		1		1			

Table S2. Continued

					SVR			TVI		
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
1111	Non-haemorrhagic stroke	**99999026**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical average - Without clinical neurophysiology		4	16	41			3
1111	Non-haemorrhagic stroke	**99999027**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical average - With clinical neurophysiology		10	16	50			3
1111	Non-haemorrhagic stroke	**99999028**	CVA non-haemorrhagic/TIA/other cerebral disorders - Thrombolytic therapy - Clinical long - Without clinical neurophysiology				1			
1111	Non-haemorrhagic stroke	**99999030**	CVA non-haemorrhagic/TIA/other cerebral disorders - Thrombolytic therapy - Clinical average - Without clinical neurophysiology		1		4			
1111	Non-haemorrhagic stroke	**99999031**	CVA non-haemorrhagic/TIA/other cerebral disorders - Thrombolytic therapy - Clinical average - With clinical neurophysiology			4	2			
1111	Non-haemorrhagic stroke	**99999035**	CVA non-haemorrhagic and TIA - Ambulant average - Continuation		19	14	55			10
1111	Non-haemorrhagic stroke	**99999036**	CVA non-haemorrhagic and TIA - Ambulant average - Regular		11	15	37			3
1111	Non-haemorrhagic stroke	**99999037**	CVA non-haemorrhagic and TIA - Mild ambulant - Continuation		28	33	66			8
1111	Non-haemorrhagic stroke	**99999038**	CVA non-haemorrhagic and TIA - Mild ambulant - Regular		6	4	26			
1111	Non-haemorrhagic stroke	**110011110111**	Regular treatment outpatient		17	42	107			
1111	Non-haemorrhagic stroke	**110011110112**	Regular treatment with day admission(s)		3	2	7			
1111	Non-haemorrhagic stroke	**110011110113**	Regular treatment with clinical episodes		21	27	68			
1111	Non-haemorrhagic stroke	**110011110213**	Thrombolysis with clinical episodes			1	6			
1199	Other cerebrovascular diseases	**99999002**	Other cerebrovascular diseases - Day		1	1	1			
1199	Other cerebrovascular diseases	**99999004**	Other cerebrovascular diseases - Multidisciplinary treatment				1			

Table S2. Continued

					SVR			TVI		
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
1199	Other cerebrovascular diseases	**99999014**	Other cerebrovascular diseases - clinical neurophysiology - Continuation		3					
1199	Other cerebrovascular diseases	**99999014**	Other cerebrovascular diseases clinical neurophysiology - Continuation			5	13			
1199	Other cerebrovascular diseases	**99999015**	Other cerebrovascular diseases - clinical neurophysiology - Regular		3	14	46			1
1199	Other cerebrovascular diseases	**99999017**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical short - Without clinical neurophysiology		2		3			
1199	Other cerebrovascular diseases	**99999018**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical short - With clinical neurophysiology		1	2				
1199	Other cerebrovascular diseases	**99999022**	Other cerebrovascular diseases - Ambulant average - Continuation		6	1	8			1
1199	Other cerebrovascular diseases	**99999023**	Other cerebrovascular diseases - Ambulant average - Regular		5	8	19			
1199	Other cerebrovascular diseases	**99999026**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical average - Without clinical neurophysiology		1		5			
1199	Other cerebrovascular diseases	**99999027**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical average - With clinical neurophysiology				1			
1199	Other cerebrovascular diseases	**99999032**	Other cerebrovascular diseases - Mild ambulant - Continuation		2	2	10			
1199	Other cerebrovascular diseases	**99999033**	Other cerebrovascular diseases - Mild ambulant - Regular		18	32	61			2
1199	Other cerebrovascular diseases	**110011990111**	Regular treatment outpatient		25	63	153			
1199	Other cerebrovascular diseases	**110011990112**	Regular treatment with day admission(s)			1	3			
1199	Other cerebrovascular diseases	**110011990113**	Regular treatment with clinical episodes		1		3			
3508	Intracranial bleeding	**990916050**	Retardation/ CVA | Clinical short | Without activities Retardation specific	1						

Table S2. Continued

					SVR			TVI		
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
TIA										
1112	TIA (incl. amaurosis fugax)	**99999006**	CVA non-haemorrhagic and TIA - Day - Without clinical neurophysiology		7	10	14			2
1112	TIA (incl. amaurosis fugax)	**99999007**	CVA non-haemorrhagic and TIA - Day - With clinical neurophysiology		11	28	73			2
1112	TIA (incl. amaurosis fugax)	**99999011**	CVA non-haemorrhagic and TIA - clinical neurophysiology		1	1				
1112	TIA (incl. amaurosis fugax)	**99999016**	CVA non-haemorrhagic and TIA - clinical neurophysiology		15	39	45			2
1112	TIA (incl. amaurosis fugax)	**99999017**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical short - Without clinical neurophysiology		4	11	25			1
1112	TIA (incl. amaurosis fugax)	**99999018**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical short - With clinical neurophysiology		8	12	25			2
1112	TIA (incl. amaurosis fugax)	**99999026**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical average - Without clinical neurophysiology			1	4			
1112	TIA (incl. amaurosis fugax)	**99999027**	CVA non-haemorrhagic/TIA/other cerebral disorders - Clinical average - With clinical neurophysiology		2	5				
1112	TIA (incl. amaurosis fugax)	**99999035**	CVA non-haemorrhagic and TIA - Ambulant average - Continuation		3	5	10			2
1112	TIA (incl. amaurosis fugax)	**99999036**	CVA non-haemorrhagic and TIA - Ambulant average - Regular		11	24	21			1
1112	TIA (incl. amaurosis fugax)	**99999037**	CVA non-haemorrhagic and TIA - Mild ambulant - Continuation		6	13	15			
1112	TIA (incl. amaurosis fugax)	**99999038**	CVA non-haemorrhagic and TIA - Mild ambulant - Regular		4	6	10			
1112	TIA (incl. amaurosis fugax)	**110011120111**	Regular treatment outpatient		20	36	66			
1112	TIA (incl. amaurosis fugax)	**110011120112**	Regular treatment with day admission(s)		6	17	48			

Table S2. Continued

					SVR				TVI	
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
1112	TIA (incl. amaurosis fugax)	**110011120113**	Regular treatment with Clinical episodes		6	10	19			
1112	TIA (incl. amaurosis fugax)	**110011120122**	Multidisciplinary treatment outpatient with day admission(s)			2				
Endocarditis										
432	Endocarditis/endovascular infection	**99899009**	Inflammation of the heart - Ambulant Average/Day 1-2		16	14	17			1
432	Endocarditis/endovascular infection	**99899010**	Inflammation of the heart - Day >2/Clinical cumulative short		4	7	6			1
432	Endocarditis/endovascular infection	**99899018**	Inflammation of the heart - Mild ambulant		13	22	9			
432	Endocarditis/endovascular infection	**99899019**	Inflammation of the heart - Day >2/Clinical cumulative long			2	4			1
432	Endocarditis/endovascular infection	**99899020**	Inflammation of the heart - Day >2/Clinical cumulative average		5	4	18			
432	Endocarditis/endovascular infection	**110004321103**	Clinical tests/treatment	1	5	9	13			
702	Endocarditis	**99899012**	Inflammation of the heart - Ambulant average		41	34	40	2		1
702	Endocarditis	**99899013**	Inflammation of the heart - Day/Clinical cumulative short		33	30	36			3
702	Endocarditis	**99899026**	Inflammation of the heart - Mild ambulant		9	17	13			
702	Endocarditis	**99899027**	Inflammation of the heart - Day/Clinical cumulative long		26	27	41			2
702	Endocarditis	**99899028**	Inflammation of the heart - Day/Clinical cumulative average		30	50	66			2
702	Endocarditis	**110007020101**	Regular treatment/no treatment outpatient		5	6	7			
702	Endocarditis	**110007020103**	Regular treatment/no treatment with Clinical episodes	1	64	69	96			
702	Endocarditis	**110007020104**	Regular treatment/no treatment single outpatient		1	1	3			

Table S2. Continued

					SVR			TVI		
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
3407	Endocarditis	**990016084**	Other cardiovascular diagnoses | Ambulant average/ Day	1						
3407	Endocarditis	**990016087**	Other cardiovascular diagnoses | Clinical average	1						
3407	Endocarditis	**990516038**	Other cardiologic diagnoses | Clinical average | Without Other cardiologic activities	2						
Myocardial infarction										
204	STEMI	**99499019**	Ischaemia with/without damage - Mild ambulant		1					
204	STEMI	**99499020**	Ischaemia with damage - Day/Clinical cumulative short			2	7			
204	STEMI	**99499028**	Ischaemia with damage - Day/Clinical cumulative average		1	4	7			
204	STEMI	**979001083**	Percutaneous coronary intervention class 4 | Without hospital stay		2	2	1			
204	STEMI	**979001084**	Percutaneous coronary intervention class 4 | With hospital stay		1	2	5			
204	STEMI	**979001097**	Percutaneous coronary intervention class 2 | With hospital stay				1			
204	STEMI	**979001219**	Percutaneous coronary intervention class 4 | With hospital stay		1		3			2
204	STEMI	**979001220**	Percutaneous coronary intervention class 4 | Without hospital stay		2	2	1			
204	STEMI	**979001223**	Percutaneous coronary intervention class 2 | With hospital stay			1	2			
204	STEMI	**110002040103**	Regular treatment/no treatment with clinical episodes		4	1	10			
204	STEMI	**110002040223**	PCI treatment class 2 with clinical episodes				1			
204	STEMI	**110002040231**	PCI treatment class 3 outpatient				1			
204	STEMI	**110002040233**	PCI treatment class 3 with clinical episodes				1			

Table S2. Continued

					SVR			TVI		
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
204	STEMI	**110002040241**	PCI treatment class 4 outpatient		1		2			
204	STEMI	**110002040242**	PCI treatment class 4 with day admission(s)			2	2			
204	STEMI	**110002040243**	PCI treatment class 4 with clinical episodes		3	3	8			
205	NSTEMI	**99499019**	Ischaemia with/without damage - Mild ambulant		1	2	6			
205	NSTEMI	**99499020**	Ischaemia with damage - Day/Clinical cumulative short		13	16	38			
205	NSTEMI	**99499027**	Ischaemia with damage - Day/Clinical cumulative long		1	1				
205	NSTEMI	**99499028**	Ischaemia with damage - Day/Clinical cumulative average		6	18	40			2
205	NSTEMI	**979001083**	Percutaneous coronary intervention class 4 | Without hospital stay			1	4			
205	NSTEMI	**979001084**	Percutaneous coronary intervention class 4 | With hospital stay		1	1				
205	NSTEMI	**979001096**	Percutaneous coronary intervention class 2 | Without hospital stay			1				
205	NSTEMI	**979001104**	Percutaneous coronary intervention class 1 | With hospital stay			1	3			
205	NSTEMI	**979001219**	Percutaneous coronary intervention class 4 | With hospital stay		1	4	6			1
205	NSTEMI	**979001221**	Percutaneous coronary intervention class 3 | With hospital stay		1	2	3			
205	NSTEMI	**979001222**	Percutaneous coronary intervention class 3 | Without hospital stay		1					
205	NSTEMI	**979001223**	Percutaneous coronary intervention class 2 | With hospital stay		1	1	1			
205	NSTEMI	**979001224**	Percutaneous coronary intervention class 2 | Without hospital stay		1		1			
205	NSTEMI	**979001226**	Percutaneous coronary intervention class 1 | Without hospital stay		1					

Table S2. Continued

					SVR			TVI		
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
205	NSTEMI	**110002050103**	Regular treatment/no treatment with Clinical episodes		4	14	39			
205	NSTEMI	**110002050211**	PCI treatment class 1 outpatient			1				
205	NSTEMI	**110002050212**	PCI treatment class 1 with day admission(s)				1			
205	NSTEMI	**110002050213**	PCI treatment class 1 with clinical episodes				1			
205	NSTEMI	**110002050233**	PCI treatment class 3 with clinical episodes			1	1			
205	NSTEMI	**110002050241**	PCI treatment class 4 outpatient		1					
205	NSTEMI	**110002050243**	PCI treatment class 4 with clinical episodes				2			
Pacemaker implantation										
301	Acute heart failure	**99899030**	Pacemaker surgery biventricular - with hospital stay				1			
301	Acute heart failure	**99899055**	Pacemaker surgery other - without hospital stay				1			
301	Acute heart failure	**99899058**	Pacemaker surgery 1 and 2 pacing leads pacemaker - with hospital stay			2	3			1
302	Chronic heart failure	**99899029**	Pacemaker surgery biventricular - without hospital stay				1			
302	Chronic heart failure	**99899030**	Pacemaker surgery biventricular - with hospital stay			3	7			1
302	Chronic heart failure	**99899055**	Pacemaker surgery other - without hospital stay				1			
302	Chronic heart failure	**99899055**	Pacemaker surgery other - without hospital stay							1
302	Chronic heart failure	**99899056**	Pacemaker surgery other - with hospital stay		3					
302	Chronic heart failure	**99899056**	Pacemaker surgery other - with hospital stay			1	2			
302	Chronic heart failure	**99899057**	Pacemaker surgery 1 and 2 pacing leads pacemaker - without hospital stay			1				
302	Chronic heart failure	**99899058**	Pacemaker surgery 1 and 2 pacing leads pacemaker - with hospital stay				9			1

Table S2. Continued

					SVR				TVI	
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
302	Chronic heart failure	**110003020111**	Regular treatment with PM implantation outpatient				1			
302	Chronic heart failure	**110003020113**	Regular treatment with PM with clinical periods				6			
401	Atrium fibrillation / flutter	**99899030**	Pacemaker surgery biventricular - with hospital stay		1	1				
401	Atrium fibrillation / flutter	**99899057**	Pacemaker surgery 1 and 2 pacing leads pacemaker - without hospital stay			2	5			1
401	Atrium fibrillation / flutter	**99899058**	Pacemaker surgery 1 and 2 pacing leads pacemaker - with hospital stay		1	5	18			
401	Atrium fibrillation / flutter	**110004010111**	Regular treatment with PM implantation outpatient				1			
401	Atrium fibrillation / flutter	**110004010113**	Regular treatment with PM with clinical periods		5	2	18			
402	Other supraventricular arrhythmias	**99899030**	Pacemaker surgery biventricular - with hospital stay				1			
402	Other supraventricular arrhythmias	**99899057**	Pacemaker surgery 1 and 2 pacing leads pacemaker - without hospital stay				2			
402	Other supraventricular arrhythmias	**99899058**	Pacemaker surgery 1 and 2 pacing leads pacemaker - with hospital stay		1	1	3			2
402	Other supraventricular arrhythmias	**110004020111**	Regular treatment with PM implantation outpatient				1			
402	Other supraventricular arrhythmias	**110004020113**	Regular treatment with PM with clinical periods			1	2			
403	Ventricular arrhythmias	**99899055**	Pacemaker surgery other - without hospital stay				1			
403	Ventricular arrhythmias	**99899056**	Pacemaker surgery other - with hospital stay		2	1	1			
403	Ventricular arrhythmias	**99899057**	Pacemaker surgery 1 and 2 pacing leads pacemaker - without hospital stay			1	1			1
403	Ventricular arrhythmias	**99899058**	Pacemaker surgery 1 and 2 pacing leads pacemaker - with hospital stay		1	1	1			1

Table S2. Continued

					SVR				TVI	
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
404	Conduction disorders	**99899029**	Pacemaker surgery biventricular - without hospital stay		1	1	1			
404	Conduction disorders	**99899030**	Pacemaker surgery biventricular - with hospital stay			5	1			
404	Conduction disorders	**99899055**	Pacemaker surgery other - without hospital stay		1	2	3			
404	Conduction disorders	**99899056**	Pacemaker surgery other - with hospital stay		2	1	6			
404	Conduction disorders	**99899057**	Pacemaker surgery 1 and 2 pacing leads pacemaker - without hospital stay		14	30	50			9
404	Conduction disorders	**99899058**	Pacemaker surgery 1 and 2 pacing leads pacemaker - with hospital stay		31	59	203	2	1	38
404	Conduction disorders	**110004040111**	Regular treatment with PM implantation outpatient		10	17	25			
404	Conduction disorders	**110004040112**	Regular treatment with PM implantation with day admission(s)		1	1	1			
404	Conduction disorders	**110004040113**	Regular treatment with PM with Clinical periods		27	52	152			
409	Other arrhythmias	**99899055**	Pacemaker surgery other - without hospital stay			1				
409	Other arrhythmias	**99899056**	Pacemaker surgery other - with hospital stay			1	1			
409	Other arrhythmias	**99899057**	Pacemaker surgery 1 and 2 pacing leads pacemaker - without hospital stay		1	1	2			
409	Other arrhythmias	**99899058**	Pacemaker surgery 1 and 2 pacing leads pacemaker - with hospital stay			2	1			1
409	Other arrhythmias	**110004090111**	Regular treatment with PM implantation outpatient			3	2			
409	Other arrhythmias	**110004090113**	Regular treatment with PM with Clinical periods		5		9			
2220	Pacemaker implantation	**99899021**	Implantation biventricular pacemaker - without hospital stay	1						

Table S2. Continued

					SVR			TVI		
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
2220	Pacemaker implantation	**99899022**	Implantation biventricular pacemaker - with hospital stay		1					
2220	Pacemaker implantation	**99899041**	Pacemaker surgery other - without hospital stay		1	5	12			
2220	Pacemaker implantation	**99899042**	Pacemaker surgery other - with hospital stay	2		1	1			
2220	Pacemaker implantation	**99899043**	Implantation 1 and 2 pacing leads pacemaker - without hospital stay		2					
2220	Pacemaker implantation	**99899044**	Implantation 1 and 2 pacing leads pacemaker - with hospital stay	1						
2220	Pacemaker implantation	**110022200110**	First surgery		2	4	2			
2390	Implantation bipolar pacemaker	**99899041**	Pacemaker surgery other - without hospital stay		1		2			
2390	Implantation bipolar pacemaker	**99899042**	Pacemaker surgery other - with hospital stay		1		1			
2390	Implantation bipolar pacemaker	**99899044**	Implantation 1 and 2 pacing leads pacemaker - with hospital stay		1					
Re-intervention										
501	Heart defect	**979001188**	Transcatheter valve implantation - Non-coronary intervention class 3 - With hospital stay		2	5	24	1		9
502	Congenital heart defect	**979001188**	Transcatheter valve implantation - Non-coronary intervention class 3 - With hospital stay	1						
2325	Aortic valve replacement (AVR)	**979001027**	Two/Multiple valve surgery – without hospital stay				1			
2325	Aortic valve replacement (AVR)	**979001028**	Two/Multiple valve surgery – with hospital stay		1		1			
2325	Aortic valve replacement (AVR)	**979001038**	Isolated valve surgery – with hospital stay		6	5	12			
2325	Aortic valve replacement (AVR)	**979001188**	Transcatheter valve implantation - Non-coronary intervention class 3 - With hospital stay			1				

Table S2. Continued

					SVR				TVI	
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
2325	Aortic valve replacement (AVR)	**979001193**	Valve surgery - 1 cost unit		10					
2325	Aortic valve replacement (AVR)	**979001189**	Transcatheter valve implantation - Non-coronary intervention class 3 - Without hospital stay		1		1			6
2325	Aortic valve replacement (AVR)	**979001192**	Valve surgery - 2 cost units		1					
2325	Aortic valve replacement (AVR)	**979001193**	Valve surgery - 1 cost unit			15	9		1	18
2325	Aortic valve replacement (AVR)	**110023250120**	First surgery with implantation	1		1	2			
2325	Aortic valve replacement (AVR)	**110023250220**	Reoperation with implantation		6	12	11			
2335	Mitral valve replacement (MVR)	**979001027**	Two/Multiple valve surgery – without hospital stay			1				
2335	Mitral valve replacement (MVR)	**979001028**	Two/Multiple valve surgery – with hospital stay		1					
2335	Mitral valve replacement (MVR)	**979001038**	Isolated valve surgery – with hospital stay		1	4	1			
2335	Mitral valve replacement (MVR)	**979001188**	Transcatheter valve implantation - Non-coronary intervention class 3 - With hospital stay			1				
2335	Mitral valve replacement (MVR)	**979001192**	Valve surgery - 2 cost units				1			
2335	Mitral valve replacement (MVR)	**979001193**	Valve surgery - 1 cost unit	2	4	2	3			1
2335	Mitral valve replacement (MVR)	**110023350120**	First surgery with implantation				1			
2335	Mitral valve replacement (MVR)	**110023350210**	Reoperation		1					
2335	Mitral valve replacement (MVR)	**110023350220**	Reoperation with implantation		4	3	5			
2340	Pulmonary valve repair / replacement	**979001027**	Two/Multiple valve surgery – without hospital stay	1						
2340	Pulmonary valve repair / replacement	**979001028**	Two/Multiple valve surgery – with hospital stay	3						
2340	Pulmonary valve repair / replacement	**979001193**	Valve surgery - 1 cost unit	4				1		
2340	Pulmonary valve repair / replacement	**110023400120**	First surgery with implantation	1						

Table S2. Continued

					SVR			TVI		
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
2340	Pulmonary valve repair / replacement	**110023400220**	Reoperation with implantation	1	2					
2410	Tricuspid valve repair / replacement	**979001028**	Two/Multiple valve surgery – with hospital stay				1			
2410	Tricuspid valve repair / replacement	**979001038**	Isolated valve surgery – with hospital stay		1					
2410	Tricuspid valve repair / replacement	**979001192**	Valve surgery - 2 cost units				1			
2410	Tricuspid valve repair / replacement	**979001193**	Valve surgery - 1 cost unit		1					
2410	Tricuspid valve repair / replacement	**110024100210**	Reoperation	1						
2410	Tricuspid valve repair / replacement	**110024100220**	Reoperation with implantation		1	1				
2415	CABG (1 art) + MVR	**979001192**	Valve surgery - 2 cost units		1					
2420	AVR + MVR	**979001028**	Two/Multiple valve surgery – with hospital stay			1				
2420	AVR + MVR	**979001192**	Valve surgery - 2 cost units		1					
2420	AVR + MVR	**979001192**	Valve surgery - 2 cost units				1			
2420	AVR + MVR	**110024200220**	Reoperation with implantation		1	2				
2425	CABG (1 art) + AVR	**979001045**	Isolated valve surgery with CABG – without hospital stay			1				
2425	CABG (1 art) + AVR	**979001046**	Isolated valve surgery with CABG – with hospital stay			1				
2425	CABG (1 art) + AVR	**979001193**	Valve surgery - 1 cost unit				1			
2425	CABG (1 art) + AVR	**110024250220**	Reoperation with implantation		1		4			
2435	Tetralogy of Fallot	**979001009**	Congenital heart surgery with ECC (complex) – without hospital stay	1						
2435	Tetralogy of Fallot	**979001010**	Congenital heart surgery with ECC (complex) – with hospital stay	2						

Table S2. Continued

					SVR				TVI	
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
2435	Tetralogy of Fallot	**979001210**	Congenital heart surgery with ECC (complex) – without hospital stay	2						
2435	Tetralogy of Fallot	**110024350210**	Reoperation	2						
2465	MVR + TPL	**979001028**	Two/Multiple valve surgery – with hospital stay		1					
2465	MVR + TPL	**979001191**	Valve surgery - 3 cost units		1					
2465	MVR + TPL	**979001192**	Valve surgery - 2 cost units			2				
2465	MVR + TPL	**110024650220**	Reoperation with implantation		2		1			
2475	Left ventricle repair+AVR/MVR	**979001037**	Isolated valve surgery – without hospital stay				1			
2545	Bentall	**979001067**	Surgery ascending aorta with a valve – without hospital stay		1	1				
2545	Bentall	**979001068**	Surgery ascending aorta with a valve – with hospital stay		1	1	2			
2545	Bentall	**110025450220**	Reoperation with implantation		3	1	1			
2565	AVR + MVR + TPL	**110025650220**	Reoperation with implantation		1					
2570	CABG (2 art) + AVR	**979001079**	Non-coronary heart intervention - without hospital stay				1			
2570	CABG (2 art) + AVR	**979001192**	Valve surgery - 2 cost units				1			
2570	CABG (2 art) + AVR	**979001193**	Valve surgery - 1 cost unit				1			
2575	AVR + MPL	**979001028**	Two/Multiple valve surgery – with hospital stay		1					
2575	AVR + MPL	**979001192**	Valve surgery - 2 cost units		1	1	1			
2575	AVR + MPL	**110025750110**	First surgery		1					
2575	AVR + MPL	**110025750220**	Reoperation with implantation		1					
2580	AVR + HOCM	**979001193**	Valve surgery - 1 cost unit							1
2645	MPL + AVR + CABG	**979001191**	Valve surgery - 3 cost units				1			
2645	MPL + AVR + CABG	**979001193**	Valve surgery - 1 cost unit				1			

Table S2. Continued

					SVR				TVI	
Diagnosis code	**Description diagnosis**	**Treatment code**	**Description treatment**	**Children**	**Young adults**	**Middle aged**	**Elderly**	**Young adults**	**Middle aged**	**Elderly**
2660	Aortic root + MVR/MPL	**979001057**	Surgery ascending aorta with two or more valves – without hospital stay		1					
2660	Aortic root + MVR/MPL	**979001058**	Surgery ascending aorta with two or more valves – with hospital stay				1			
2660	Aortic root + MVR/MPL	**110026600220**	Reoperation with implantation			1				
2680	AVR + Ascending aorta	**979001067**	Surgery ascending aorta with a valve – without hospital stay				1			
2680	AVR + Ascending aorta	**979001068**	Surgery ascending aorta with a valve – with hospital stay		1	2	2			
2680	AVR + Ascending aorta	**110026800220**	Reoperation with implantation		1		1			
2695	AVR + MVR +/- TPL	**979001028**	Two/Multiple valve surgery – with hospital stay			2				
2695	AVR + MVR +/- TPL	**979001192**	Valve surgery - 2 cost units		1	1	1			
2695	AVR + MVR +/- TPL	**110026950220**	Reoperation with implantation			1				
2770	Aortic root + CABG + MPL/MVR	**979001058**	Surgery ascending aorta with two or more valves – with hospital stay				2			
2770	Aortic root + CABG + MPL/MVR	**110027700210**	Reoperation		1					
2785	Maze+CABG of AVR+MPL +/- TPL	**979001191**	Valve surgery - 3 cost units			1				
2785	Maze+CABG of AVR+MPL +/- TPL	**110027850120**	First surgery with implantation		1					
2790	AVR+ascending aorta+MPL+/- TPL	**979001058**	Surgery ascending aorta with two or more valves – with hospital stay		1	1	1			

CABG: coronary artery bypass grafting. AVR: aortic valve replacement. MVR: mitral valve replacement. MPL: mitral valve repair. TPL: tricuspid valve repair. HOCM: Hypertrophic Obstructive Cardiomyopathy. ECC: Extracorporeal Circulation.

Table S3. Healthcare costs of children (0-18 years) after heart valve intervention compared to controls

Children (0-18 years)	Costs (€), mean (CI)		
Year 1	Patients	Controls	Difference
General practitioner	168 (155-184)	103 (101-105)	65 (51-80)
Hospital costs (in- and outpatient)[1]	24,085 (22,909-25,229)	461 (429-497)	23,625 (22,451-24,751)
ICU stay	6,403 (4,749-8,646)	54 (31-81)	6,350 (4,695-8,580)
Medicines expensive drugs list	0 (0-0)	5 (0-14)	-5 (-14-0)
Primary care diagnostics	98 (67-131)	13 (12-14)	85 (54-119)
Other specialized care	459 (317-636)	30 (24-37)	429 (287-610)
Pharmaceuticals	1,602 (1,257-1,971)	67 (56-82)	1,534 (1,192-1,907)
Paramedical care	359 (294-433)	48 (44-53)	311 (246-385)
Patient transport	249 (186-320)	11 (08-14)	238 (175-310)
Home care	284 (25-744)	4 (0-12)	279 (20-740)
Nursing homes	0 (0-0)	0 (0-0)	0 (0-0)
Geriatric rehabilitation care	0 (0-0)	0 (0-0)	0 (0-0)
Total costs	**33,707 (31,103-36,595)**	**796 (739-861)**	**32,912 (30,302-35,800)**
Year 2			
General practitioner	157 (141-175)	112 (111-114)	45 (28-62)
Hospital costs (in- and outpatient)	3,244 (2,570-3,969)	460 (422-502)	2,784 (2,108-3,521)
ICU stay	217 (104-359)	47 (24-76)	170 (49-314)
Medicines expensive drugs list	0 (0-0)	5 (0-14)	-5 (-14-0)
Primary care diagnostics	88 (58-125)	14 (13-15)	75 (43-110)
Other specialized care	105 (44-185)	27 (22-34)	78 (15-158)
Pharmaceuticals	888 (535-1,284)	70 (58-85)	818 (464-1,214)
Paramedical care	295 (211-396)	51 (46-56)	244 (158-344)
Patient transport	72 (40-110)	10 (8-14)	62 (30-99)
Home care	429 (0-1,455)	4 (0-12)	425 (-9-1,450)
Nursing homes	0 (0-0)	0 (0-0)	0 (0-0)
Geriatric rehabilitation care	0 (0-0)	0 (0-0)	0 (0-0)
Total costs	**5,495 (4,108-7,207)**	**802 (741-869)**	**4,694 (3,305-6,419)**
Year 3			
General practitioner	148 (132-166)	116 (114-118)	32 (16-50)
Hospital costs (in- and outpatient)	3,313 (2,291-4,423)	446 (400-498)	2,868 (1,833-3,980)
ICU stay	35 (0-92)	40 (14-79)	-5 (-59-57)
Medicines expensive drugs list	0 (0-0)	5 (0-14)	-5 (-14-00)
Primary care diagnostics	113 (68-162)	14 (13-15)	98 (54-149)
Other specialized care	69 (7-182)	26 (19-34)	43 (-19-153)
Pharmaceuticals	296 (148-480)	69 (57-83)	227 (80-418)
Paramedical care	193 (123-275)	56 (50-62)	137 (66-219)
Patient transport	66 (25-120)	9 (7-12)	57 (16-111)
Home care	781 (47-1,950)	4 (0-12)	777 (42-1,944)
Nursing homes	0 (0-0)	0 (0-0)	0 (0-0)
Geriatric rehabilitation care	0 (0-0)	0 (0-0)	0 (0-0)
Total costs	**5,015 (3,434-6,810)**	**786 (713-871)**	**4,229 (2,657-6,045)**

ICU: intensive care unit. CI: 95% confidence interval. [1]Including DBC costs of the heart valve intervention.

Table S4. Healthcare costs of young adults (19-60 years) after heart valve intervention compared to controls

Young adults (19-60 years)	Costs (€), mean (CI)		
Year 1	Patients	Controls	Difference
General practitioner	220 (214-227)	142 (141-143)	79 (72-85)
Hospital costs (in- and outpatient)[1]	29,558 (28,932-30,217)	1,525 (1,484-1,568)	28,033 (27,410-28,696)
ICU stay	7,070 (6,452-7,737)	76 (67-86)	6,993 (6,375-7,662)
Medicines expensive drugs list	179 (77-299)	131 (112-153)	49 (-54-170)
Primary care diagnostics	496 (472-523)	89 (83-96)	407 (383-435)
Other specialized care	520 (471-582)	51 (36-69)	470 (416-531)
Pharmaceuticals	1,057 (966-1,157)	649 (630-668)	408 (312-510)
Paramedical care	79 (69-91)	46 (43-49)	33 (22-45)
Patient transport	602 (565-640)	55 (51-58)	547 (511-586)
Home care	145 (88-215)	103 (86-122)	42 (-16-112)
Nursing homes	30 (11-54)	58 (40-77)	-28 (-57-1)
Geriatric rehabilitation care[2]	229 (87-419)	20 (15-26)	209 (66-398)
Total costs	**40,186 (39,145-41,334)**	**2,944 (2,870-3,021)**	**37,242 (36,181-38,384)**
Year 2			
General practitioner	172 (165-178)	143 (142-145)	28 (22-35)
Hospital costs (in- and outpatient)	4,560 (3,990-5,139)	1,550 (1,503-1,595)	3,010 (2,442-3,587)
ICU stay	573 (322-917)	86 (75-98)	487 (235-834)
Medicines expensive drugs list	114 (33-217)	131 (112-153)	-17 (-103-91)
Primary care diagnostics	537 (510-564)	82 (79-85)	455 (428-483)
Other specialized care	85 (64-108)	56 (36-81)	29 (-2-59)
Pharmaceuticals	859 (755-983)	642 (624-662)	216 (112-342)
Paramedical care	83 (68-99)	45 (42-47)	39 (23-55)
Patient transport	173 (136-211)	55 (52-59)	118 (81-157)
Home care	160 (77-263)	103 (86-122)	57 (-28-162)
Nursing homes	150 (13-361)	58 (40-77)	92 (-49-301)
Geriatric rehabilitation care[2]	131 (23-274)	20 (15-26)	110 (2-253)
Total costs	**7,596 (6,809-8,447)**	**2,972 (2,892-3,054)**	**4,624 (3,828-5,476)**
Year 3			
General practitioner	171 (160-183)	142 (141-144)	28 (18-40)
Hospital costs (in- and outpatient)	3,706 (3,024-4,481)	1,552 (1,500-1,602)	2,154 (1,470-2,937)
ICU stay	533 (216-936)	102 (87-118)	432 (113-834)
Medicines expensive drugs list	70 (15-146)	131 (112-153)	-61 (-120-20)
Primary care diagnostics	538 (500-577)	80 (78-82)	458 (420-497)
Other specialized care	38 (20-63)	53 (33-79)	-15 (-49-17)
Pharmaceuticals	815 (688-957)	618 (598-638)	198 (72-341)
Paramedical care	46 (28-67)	40 (38-43)	5 (-13-26)
Patient transport	148 (98-209)	56 (52-60)	92 (42-152)
Home care	189 (67-379)	103 (86-122)	86 (-40-277)
Nursing homes	296 (33-644)	58 (40-77)	237 (-25-583)
Geriatric rehabilitation care[2]	84 (2-213)	20 (15-26)	63 (-19-195)
Total costs	**6,633 (5,587-7,751)**	**2,955 (2,873-3,043)**	**3,678 (2,641-4,824)**

ICU: intensive care unit. CI: 95% confidence interval. [1]Including DBC costs of the heart valve intervention. [2]The proportion of patients using geriatric rehabilitation care of the "young" adults was small (<1%) and their mean age was above 50 years.

Table S5. Healthcare costs of middle aged patients (61-70 years) after heart valve intervention compared to controls

Middle aged patients (61-70 years)	Costs (€), mean (CI)		
Year 1	Patients	Controls	Difference
General practitioner	254 (248-260)	173 (172-174)	81 (75-87)
Hospital costs (in- and outpatient)[1]	30,108 (29,635-30,560)	2,384 (2,342-2,425)	27,724 (27,244-28,175)
ICU stay	7,523 (6,976-8,091)	140 (129-151)	7,383 (6,836-7,955)
Medicines expensive drugs list	225 (93-407)	172 (153-191)	53 (-84-239)
Primary care diagnostics	321 (307-336)	125 (118-132)	197 (181-213)
Other specialized care	407 (382-432)	49 (37-63)	358 (327-387)
Pharmaceuticals	1,148 (1,086-1,221)	855 (839-871)	293 (230-368)
Paramedical care	89 (79-99)	75 (73-78)	13 (4-23)
Patient transport	679 (647-711)	82 (79-85)	598 (566-630)
Home care	389 (305-483)	252 (234-271)	137 (48-234)
Nursing homes	131 (59-221)	226 (201-254)	-96 (-172--5)
Geriatric rehabilitation care	424 (263-592)	79 (71-88)	344 (182-513)
Total costs	**41,699 (40,766-42,594)**	**4,612 (4,536-4,693)**	**37,086 (36,158-38,011)**
Year 2			
General practitioner	209 (202-216)	176 (175-177)	32 (25-39)
Hospital costs (in- and outpatient)	4,483 (4,077-4,902)	2,428 (2,383-2,471)	2,056 (1,647-2,476)
ICU stay	522 (300-836)	162 (148-177)	359 (137-676)
Medicines expensive drugs list	206 (90-351)	172 (153-191)	34 (-84-181)
Primary care diagnostics	285 (268-303)	119 (117-122)	166 (149-184)
Other specialized care	48 (36-61)	53 (37-72)	-05 (-28-15)
Pharmaceuticals	1,051 (969-1,149)	852 (836-869)	199 (114-299)
Paramedical care	105 (90-123)	74 (71-77)	31 (15-48)
Patient transport	149 (126-174)	85 (82-88)	64 (41-89)
Home care	279 (188-388)	252 (234-271)	27 (-67-138)
Nursing homes	270 (92-500)	226 (201-254)	43 (-135-282)
Geriatric rehabilitation care	216 (90-385)	79 (71-88)	136 (13-307)
Total costs	**7,823 (7,195-8,559)**	**4,679 (4,599-4,763)**	**3,144 (2,488-3,892)**
Year 3			
General practitioner	207 (197-217)	177 (175-178)	30 (20-40)
Hospital costs (in- and outpatient)	4,050 (3,553-4,567)	2,434 (2,386-2,483)	1,615 (1,120-2,147)
ICU stay	609 (311-954)	192 (173-212)	416 (119-765)
Medicines expensive drugs list	113 (51-191)	172 (153-191)	-59 (-128-21)
Primary care diagnostics	301 (278-329)	119 (117-121)	182 (159-211)
Other specialized care	36 (25-49)	50 (32-73)	-14 (-40-8)
Pharmaceuticals	1,049 (923-1,208)	823 (807-840)	227 (99-389)
Paramedical care	76 (55-97)	67 (64-70)	8 (-12-29)
Patient transport	170 (136-207)	89 (85-93)	81 (47-118)
Home care	510 (373-667)	252 (234-271)	257 (118-418)
Nursing homes	489 (223-814)	226 (201-254)	262 (-4-593)
Geriatric rehabilitation care	156 (54-286)	79 (71-88)	77 (-25-205)
Total costs	**7,764 (6,913-8,703)**	**4,681 (4,594-4,770)**	**3,083 (2,226-4,019)**

ICU: intensive care unit. CI: 95% confidence interval. [1]Including DBC costs of the heart valve intervention.

Table S6. Healthcare costs of elderly patients (>70 years) after heart valve intervention compared to controls

Elderly patients (>70 years)	Costs (€), mean (CI)		
Year 1	Patients	Controls	Difference
General practitioner	319 (314-324)	240 (239-241)	79 (73-84)
Hospital costs (in- and outpatient)[1]	30,368 (30,096-30,645)	2,920 (2,891-2,949)	27,448 (27,180-27,727)
ICU stay	7,810 (7,466-8,172)	152 (145-159)	7,659 (7,312-8,021)
Medicines expensive drugs list	76 (46-113)	113 (101-129)	-37 (-73-2)
Primary care diagnostics	275 (266-284)	137 (136-139)	137 (128-147)
Other specialized care	293 (280-308)	35 (31-39)	259 (245-274)
Pharmaceuticals	1,136 (1,107-1,169)	998 (988-1,009)	138 (107-171)
Paramedical care	112 (104-120)	102 (99-104)	11 (2-19)
Patient transport	751 (731-771)	139 (136-141)	612 (592-633)
Home care	1,199 (1,080-1,321)	1,330 (1,295-1,368)	-131 (-254--6)
Nursing homes	866 (705-1,041)	2,761 (2,699-2,830)	-1,894 (-2,068--1,710)
Geriatric rehabilitation care	1,262 (1,068-1,466)	310 (298-322)	952 (761-1,157)
Total costs	**44,470 (43,853-45,102)**	**9,236 (9,148-9,330)**	**35,233 (34,624-35,884)**
Year 2			
General practitioner	278 (271-285)	244 (243-245)	34 (27-41)
Hospital costs (in- and outpatient)	4,436 (4,203-4,674)	2,938 (2,907-2,969)	1,498 (1,268-1,741)
ICU stay	364 (273-468)	171 (163-180)	192 (104-298)
Medicines expensive drugs list	76 (41-118)	113 (101-129)	-37 (-75-6)
Primary care diagnostics	212 (203-222)	141 (139-143)	71 (62-81)
Other specialized care	41 (34-49)	32 (28-39)	8 (-1-17)
Pharmaceuticals	1,158 (1,116-1,205)	991 (980-1,002)	168 (124-215)
Paramedical care	131 (118-144)	98 (96-101)	33 (20-46)
Patient transport	199 (181-217)	144 (141-146)	55 (37-73)
Home care	1,269 (1,106-1,444)	1,330 (1,295-1,368)	-61 (-232-120)
Nursing homes	1,763 (1,422-2,126)	2,761 (2,699-2,830)	-997 (-1,341--631)
Geriatric rehabilitation care	552 (400-713)	310 (298-322)	241 (92-405)
Total costs	**10,478 (9,951-11,051)**	**9,273 (9,181-9,367)**	**1,205 (670-1,790)**
Year 3			
General practitioner	267 (259-276)	243 (242-245)	24 (15-33)
Hospital costs (in- and outpatient)	4,311 (3,955-4,686)	2,885 (2,850-2,920)	1,425 (1,077-1,815)
ICU stay	320 (196-486)	198 (186-209)	122 (-4-289)
Medicines expensive drugs list	97 (51-154)	113 (101-129)	-16 (-65-44)
Primary care diagnostics	196 (186-206)	139 (138-141)	56 (46-67)
Other specialized care	22 (16-30)	25 (21-31)	-3 (-12-6)
Pharmaceuticals	1,132 (1,081-1,183)	957 (946-969)	175 (123-227)
Paramedical care	83 (69-98)	89 (86-91)	-6 (-20-10)
Patient transport	210 (184-238)	150 (147-153)	60 (34-89)
Home care	1,457 (1,283-1,647)	1,330 (1,295-1,368)	127 (-47-323)
Nursing homes	1,990 (1,636-2,366)	2,761 (2,699-2,830)	-770 (-1,132--389)
Geriatric rehabilitation care	618 (471-778)	310 (298-322)	307 (160-469)
Total costs	**10,701 (10,031-11,384)**	**9,200 (9,108-9,298)**	**1,501 (821-2,184)**

ICU: intensive care unit. CI: 95% confidence interval. [1]Including DBC costs of the heart valve intervention.

Table S7. Generalized linear model for the intervention costs (including ICU costs)

	SVR (n=17,963)			TVI (n=912)		
Parameter	**β**	**95% CI**	**P-value**	**β**	**95% CI**	**P-value**
Intercept	20,301	19,840-20,761	<.0001	31,157	29,126-33,188	<.0001
Valve position (compared to aortic)						
Pulmonary	-1,120	-2,368-128	0.079			
Mitral	2,879	2,361-3,398	<.0001			
Aortic and mitral	8,534	7,444-9,624	<.0001			
Tricuspid	6,250	4,680-7,819	<.0001			
Concomitant procedures (compared to isolated valve replacement)						
CABG	5,678	5,357-5,999	<.0001			
Valve repair	8,919	8,239-9,600	<.0001			
Maze + CABG or valve repair	8,354	7,521-9,187	<.0001			
Bentall	6,563	5,711-7,416	<.0001			
Aortic ascending aorta	4,635	3,752-5,519	<.0001			
Tetralogy of Fallot	2,299	785-3,812	0.003			
Aortic ascending aorta + valve repair	12,098	9,641-14,554	<.0001			
HOCM	9,026	6,599-11,454	<.0001			
Aortic root	12,768	8,926-16,610	<.0001			
Aortic root + CABG	6,358	3,067-9,650	0.000			
Left ventricle repair	6,023	1,303-10,743	0.012			
Age (compared to elderly)						
Children (0-18 years)	281	-1,144-1,706	0.699			
Young adults (19-60 years)	83	-292-459	0.664	1,762	-896-4,419	0.194
Middle aged (61-70 years)	-110	-417-197	0.484	557	-1,199-2,313	0.534
Male	544	282-806	<.0001	-166	-1,101-769	0.728
Co-morbidity (compared to no co-morbidity)						
COPD, DM, kidney disease and/or HF	376	-36-787	0.074	-265	-2,166-1,636	0.785
Hypertension	-237	-647-173	0.257	-535	-2,563-1,492	0.605
Other comorbidities	-389	-959-181	0.181	-1,222	-3,970-1,526	0.384
SES[1] (compared to highest SES: 71-100)						
0-20	699	328-1,070	0.000	1,414	122-2,707	0.032
21-40	531	161-901	0.005	1,133	-250-2,516	0.108
41-70	67	-264-398	0.691	-20	-1,240-1,201	0.975
Death (within 6 months after the intervention)	14,092	13,216-14,969	<.0001	6,863	4,896-8,829	<.0001

Gamma distribution and identity link. SVR: surgical valve replacement. TVI: transcatheter valve implantation. ICU: intensive care unit. CI: confidence interval. CABG: concomitant coronary artery bypass grafting. HOCM: Hypertrophic Obstructive Cardiomyopathy. COPD: Chronic Obstructive Pulmonary Disease. DM: diabetes mellitus. HF: heart failure. SES: Socioeconomic status. [1]Higher percentiles represent higher SES.

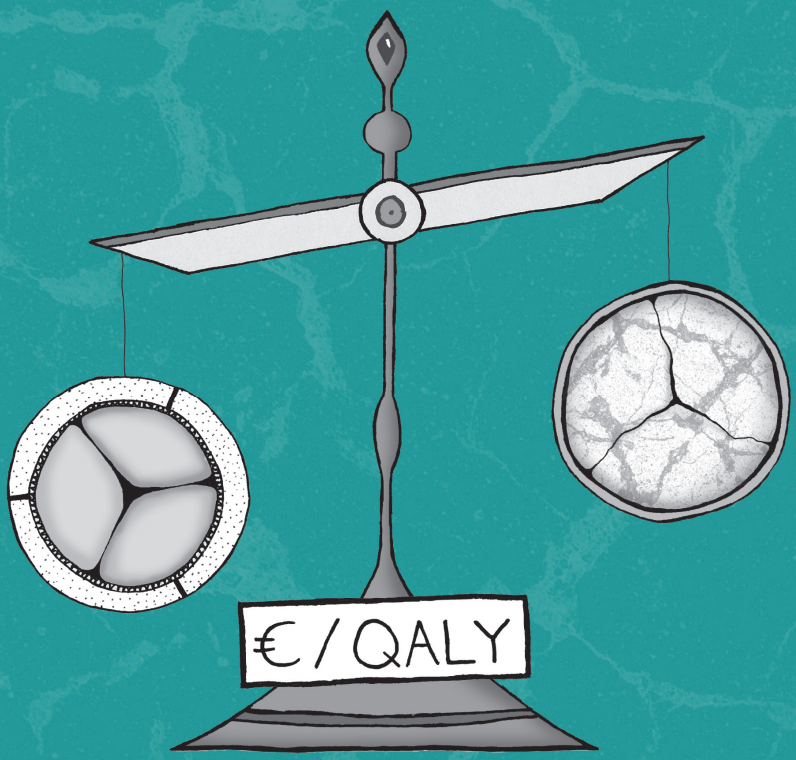
Table S8. Generalized linear model for complication costs (including ICU costs)

Parameter	β	95% CI	P-value	β	95% CI	P-value
	Acute kidney injury (AKI)			**Atrial fibrillation (AF)**		
Intercept	8,211	4,372-12,050	<.0001	1,147	993-1,302	<.0001
Age (compared to elderly)						
Children (0-18 years)	-3,475	-11,704-4,755	0.408	1,479	-47-3,006	0.058
Young adults (19-60 years)	1,100	-2,260-4,461	0.521	263	138-389	<.0001
Middle aged (61-70 years)	-1,012	-2,913-889	0.297	84	00-168	0.051
Male	1,972	114-3,830	0.038	76	01-150	0.046
Co-morbidity (compared to no co-morbidity)						
COPD, DM, kidney disease and/or HF	-802	-3,946-2,343	0.617	-37	-177-102	0.600
Hypertension	-3,557	-6,783--330	0.031	-123	-270-24	0.101
Other comorbidities	4,427	-4,515-13,369	0.332	-37	-258-184	0.742
SES[1] (compared to highest SES: 71-100)						
0-20	543	-2,198-3,285	0.698	15	-95-125	0.795
21-40	479	-2,227-3,186	0.729	-30	-135-74	0.573
41-70	-723	-3,290-1,844	0.581	14	-83-111	0.776
Death (within 6 months after complication)	2,188	-11-4,386	0.051	1,861	1,291-2,431	<.0001
	Stroke			**Transient ischemic attack (TIA)**		
Intercept	2,702	2,017-3,387	<.0001	1,076	803-1,349	<.0001
Age (compared to elderly)						
Children (0-18 years)	-1,590	-5,300-2,121	0.401	NA		.
Young adults (19-60 years)	284	-273-842	0.318	83	-152-319	0.488
Middle aged (61-70 years)	-169	-557-219	0.394	68	-107-242	0.446
Male	23	-319-364	0.896	-46	-202-110	0.566
Co-morbidity (compared to no co-morbidity)						
COPD, DM, kidney disease and/or HF	-380	-1,000-241	0.231	374	126-622	0.003
Hypertension	-179	-832-474	0.591	151	-88-390	0.217
Other comorbidities	-878	-1,691--65	0.034	144	-165-454	0.361
SES[1] (compared to highest SES: 71-100)						
0-20	87	-374-547	0.712	-32	-264-200	0.787
21-40	306	-208-819	0.243	-69	-305-167	0.569
41-70	208	-218-635	0.338	-83	-285-119	0.422
Death (within 6 months after complication)	2,890	1,991-3,788	<.0001	-128	-573-317	0.574
	Endocarditis			**Myocardial infarction (MI)**		
Intercept	9,574	7,160-11,988	<.0001	3,545	1,973-5,117	<.0001
Age (compared to elderly)						
Children (0-18 years)	-827	-9,011-7,357	0.843	NA		.
Young adults (19-60 years)	-819	-2,544-906	0.352	1,422	139-2,705	0.030
Middle aged (61-70 years)	-796	-2,389-798	0.328	203	-706-1,113	0.661
Male	-1,250	-2,900-400	0.138	277	-496-1,051	0.482

Table S8. Continued

Parameter	β	95% CI	P-value	β	95% CI	P-value
Co-morbidity (compared to no co-morbidity)						
COPD, DM, kidney disease and/or HF	319	-1,524-2,162	0.735	1,370	117-2,623	0.032
Hypertension	-437	-2,205-1,330	0.628	1,102	-294-2,498	0.122
Other comorbidities	-318	-3,313-2,677	0.835	1,474	-923-3,871	0.228
SES[1] (compared to highest SES: 71-100)						
0-20	-346	-2,408-1,716	0.742	-674	-1,751-403	0.220
21-40	137	-1,801-2,075	0.890	-595	-1,715-525	0.298
41-70	-1,089	-2,683-504	0.180	86	-1,047-1,219	0.882
Death (within 6 months after complication)	1,898	-387-4,183	0.104	2,990	1,515-4,466	<.0001
	Pacemaker implantation (PI)			**Re-intervention**		
Intercept	10,552	9,559-11,545	<.0001	19,461	15,592-23,331	<.0001
Age (compared to elderly)						
Children (0-18 years)	-6,071	-7,967--4,176	<.0001	-52	-5,012-4,908	0.984
Young adults (19-60 years)	-445	-1,231-341	0.267	813	-2,491-4,118	0.630
Middle aged (61-70 years)	110	-575-794	0.754	-3,082	-5,974--190	0.037
Male	-52	-588-485	0.850	-148	-2,510-2,215	0.902
Co-morbidity (compared to no co-morbidity)						
COPD, DM, kidney disease and/or HF	377	-485-1,239	0.391	4,281	655-7,907	0.021
Hypertension	584	-340-1,509	0.215	3,360	-417-7,137	0.081
Other comorbidities	726	-635-2,087	0.296	2,033	-4,114-8,179	0.517
SES[1] (compared to highest SES: 71-100)						
0-20	718	-36-1,472	0.062	239	-3,192-3,670	0.891
21-40	337	-378-1,052	0.355	1,611	-1,917-5,139	0.371
41-70	1,102	406-1,797	0.002	1,448	-1,319-4,215	0.305
Death (within 6 months after complication)	4,221	2,544-5,899	<.0001	9,492	5,011-13,973	<.0001

Gamma distribution and identity link. ICU: intensive care unit. CI: confidence interval. COPD: Chronic Obstructive Pulmonary Disease. DM: diabetes mellitus. HF: heart failure. SES: Socioeconomic status. [1]Higher percentiles: higher SES.


€/QALY

8

Early health technology assessment of tissue-engineered heart valves compared to bioprostheses in the aortic position in elderly patients

Simone A. Huygens, Isaac Corro Ramos, Carlijn V.C. Bouten, Jolanda Kluin, Shih Ting Chiu, Gary L. Grunkemeier, Johanna J.M. Takkenberg, Maureen P.M.H. Rutten-van Mölken.

Submitted.

ABSTRACT

Objective: Aortic valve disease is the most frequent indication for heart valve surgery with the highest prevalence in elderly patients. Living heart valves created inside the heart from patient's own tissue (tissue-engineered heart valves; TEHV) are foreseen to have important advantages over existing heart valve substitutes, most importantly reducing degeneration of heart valve substitutes and subsequent re-interventions. We performed early Health Technology Assessment of TEHV in elderly patients requiring surgical (SAVR) or transcatheter aortic valve implantation (TAVI) to assess the potential of TEHV in this population.

Methods: Using a patient-level simulation model, the cost-effectiveness of SAVR/TAVI with TEHV versus bioprostheses was assessed from a societal perspective. Improvements in TEHV performance, divided in durability, thrombogenicity, and infection resistance, were explored in scenario analyses to estimate quality adjusted life year (QALY) gain, cost reduction, headroom, and budget impact.

Results: Durability of TEHV had the highest impact on cost-effectiveness, followed by infection resistance. Improved TEHV performance (-50% prosthetic valve-related events) resulted in lifetime QALY gains and cost reductions of 0.131 QALY and €639 per SAVR patient and 0.043 QALY and €368 per TAVI patient versus bioprostheses, translating to headrooms of €3,255 and €2,498 for surgical and transcatheter TEHV, respectively. National savings in the first decade after implementation, varied from €2.8 to €11.2 million (SAVR) and €3.2 to €12.8 million (TAVI) for TEHV substitution rates of 25% or 100%.

Conclusions: Despite the relatively short life expectancy of elderly patients undergoing aortic valve implantation, the potential cost-effectiveness of TEHV in these patients is promising.

INTRODUCTION

Aortic valve disease is the most frequent indication for heart valve surgery.[1] Prevalence of aortic valve disease is the highest in elderly patients (stenosis 2.8%; regurgitation 2.0%), due to degeneration of the native aortic valve.[2] Aortic valve disease can be treated with medication to relieve symptoms, but can only be cured with aortic valve replacement.[3] In addition to surgical aortic valve replacement (SAVR), transcatheter aortic valve implantation (TAVI) is a less invasive alternative to replace the aortic valve for patients who are deemed inoperable or at high operable risk because of comorbidities.[3] During a TAVI procedure, a balloon or self-expanding bioprosthesis is implanted with a catheter trough an artery most frequently in the groin or underneath the collarbone. Surgical heart valve substitutes can be divided into biological (human or animal donor) and mechanical valves. In elderly patients eligible for surgery, bioprostheses (animal donor) are preferred because patients' life expectancy is usually shorter than the valve's durability and therefore patients can benefit from the advantages of bioprostheses (e.g. no need for lifelong anticoagulation).[3] However, risk of re-intervention due to limited durability of bioprostheses is not absent in elderly patients and there is an increased risk of endocarditis (i.e. infection of the heart valve) after SAVR and TAVI.[4, 5]

Tissue-engineered heart valves (TEHV) can potentially limit the disadvantages of existing heart valve substitutes.[6-9] TEHV are valve-shaped scaffolds implanted in heart that recruit cells from the bloodstream and surrounding tissues and gradually transform into a living valve while the scaffold degrades.[9] Currently, both surgical and transcatheter implantation of TEHV are explored. Preclinical studies on TEHV performance in sheep and clinical trials of tissue-engineered vascular grafts showed promising results, but results of the first-in-man clinical trial of TEHV are not available yet.[7-10] Due to the ageing population and improvements in healthcare, the number of aortic valve implantations is expected to increase, especially in elderly patients.[2, 6] Therefore, TEHV can potentially reduce the burden of existing heart valve substitutes in a large number of patients.

Before TEHV can be introduced in clinical practice, healthcare decision makers need assurance that TEHV are safe, effective and cost-effective. Moreover, information on cost-effectiveness is important during early development phases to ensure that TEHV will meet the needs of patients, professionals, and payers. In this early Health Technology Assessment (HTA) study, we estimated the potential cost-effectiveness, headroom and budget impact of TEHV in elderly patients requiring surgical or transcatheter aortic valve implantation using a patient-level simulation model.

METHODS

Study population

The study population that is simulated was sampled with replacement from existing patient databases and comprised patients of ≥70 years who underwent aortic valve implantation with bioprostheses , either SAVR or TAVI. SAVR patients were sampled from the Adult Cardiac Surgery Database (ACSD) from The Netherlands Association for Cardio-Thoracic Surgery (mean±SD age: 77.0±4.1 years). TAVI patients were sampled from Dutch health insurance claims databases (mean±SD age: 81.9±4.9 years).[11] Patient and intervention characteristics are presented in Table S1.

Patient-level simulation model

The patient-level simulation model was based on a conceptual model (Figure 1; Supplement 1).[12] The model combines fixed estimates and regression equations for different intermediate and final outcomes (Table S2-3). Final outcomes are quality adjusted life years (QALY) and costs. The model simulation starts with randomly sampling 25,000 patients from the databases specified above. The number of 25,000 sampled patients was required to get stable results. For each patient, mortality and event risks within 30 days after the intervention are calculated based on patient characteristics (SAVR) or fixed estimates (TAVI). Subsequently, time to late events and death are calculated (independent of patient characteristics). The event with the lowest predicted time value is considered to occur after which the consequences for costs and QALYs are modelled. Then, times to late events and death are recalculated. The simulation stops when death has the lowest predicted time value of all events or when patients die directly after an event. This process is repeated for all patients (Figure S1). By combining data of all simulated patients, the average difference in QALYs and costs between TEHV and bioprostheses is calculated. The model was implemented in R 3.3.2 using RStudio 1.0.136.

Model input and assumptions

Mortality and events

Mortality was divided into early mortality (≤30 days), mortality directly related to valve-related events, background mortality, and excess mortality. Background mortality was obtained for the year 2016 in the Dutch general population.[13] Excess mortality is mortality ascribed to the potential excess risk of dying of patients after heart valve interventions. This excess mortality was expressed as hazard ratio relative to background mortality (SAVR: 0.86[5]; TAVI: 1.50(Supplement 2)). This means that background mortality in SAVR patients was 14% lower than in the general population, probably due to careful selection of relatively healthy elderly to undergo SAVR while frail elderly are rejected for

surgery.[5, 14] Background mortality in TAVI patients was 50% higher than in the general population, possibly due to increased occurrence of comorbidities in TAVI patients.[15]

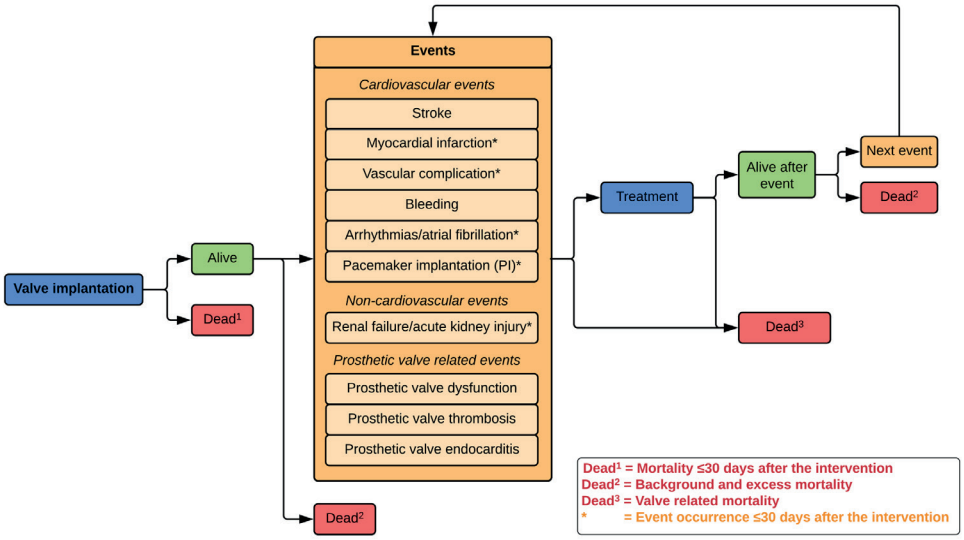


Figure 1. Conceptual model. Adaptions of the original conceptual model are discussed in Supplement 1.

The following events were included in our model during the entire simulation: stroke, bleeding, prosthetic valve dysfunction (structural valve deterioration (SVD) and non-structural valve dysfunction), -thrombosis and -endocarditis. In addition, the following events were only included within 30 days after the intervention: myocardial infarction, vascular complication, arrhythmias/atrial fibrillation, pacemaker implantation, and renal failure/acute kidney injury (Table S2).

Clinical input parameters are provided in Table 1. Risks of early mortality, stroke, renal failure, arrhythmias and myocardial infarction within 30 days after SAVR were dependent on patient and intervention characteristics, estimated using logistic regression models based on ACSD (Tables S4-8). Risks and rates of mortality and other events after SAVR and TAVI and probabilities of re-intervention or death as a direct result of events were derived from literature (references in Table 1) and were independent of patient and intervention characteristics or patient history. Time to SVD after SAVR is obtained from a Gompertz distribution fitted to a pooled Kaplan-Meier curve.[5] Time to SVD after TAVI is obtained from a lognormal distribution fitted to a published Kaplan-Meier curve.[4] These distributions had the best fit according to visual comparison, log-likelihood and Akaike information criterion. We were unable to determine distributions of other events due to limited data availability, therefore we assumed constant hazard rates by using exponential distributions.

Costs

Healthcare costs were divided into intervention costs (procedure and hospital stay), event costs, other healthcare costs (healthcare use not directly related to the heart valve intervention or initial treatment of associated events), and end of life healthcare costs (healthcare use associated with dying) (Table 2). Healthcare costs were defined as expenditures reimbursed by health insurers. Costs were dependent on patient and intervention characteristics using (multilevel) generalised linear models ((M)GLM)(Table S9)[11], except for costs of bleeding and conservative treatment of prosthetic valve-related events. We assumed most events had a permanent influence on healthcare use (e.g. lifelong follow-up with cardiologist after pacemaker implantation). Hence, other healthcare costs were assumed to be increased for the remaining patient's lifetime after most events, except for prosthetic valve-related events and re-intervention to avoid double counting of follow-up costs for the initial heart valve implantation. Other healthcare costs were estimated with the MGLM regression formula within three years after the intervention (Table S9). Beyond three years, these costs were adjusted to patient age using relative increases in total healthcare costs by age and sex of the general Dutch population.[16]

Costs beyond healthcare included productivity costs of unpaid work and informal care costs and were dependent on patient and intervention characteristics based on logistic models and GLM (Tables S10-11). Productivity costs of paid work were excluded because the vast majority (≥95%) of elderly patients undergoing SAVR or TAVI do not have paid employment.[17] Productivity costs were increased after events by assuming that patients were unable to perform their unpaid work activities during hospital admissions for bleeding and prosthetic valve-related events(Table S12), 4 months after surgical re-intervention[17], 1 month after transcatheter re-intervention[17], and 28.2 days after stroke.[18] Informal care costs were assumed to be unchanged after in-hospital treatment of bleeding and prosthetic valve-related events, because care associated with these events is provided in-hospital. After re-intervention, we assumed equal informal care costs as after the initial intervention. After stroke, we assumed that 54% of patients used informal care for 13.5 hours/week during the first half year and 8.3 hours/week during the second half year and subsequent years.[18]

Health-related quality of life

Health-related quality of life was expressed in utilities. Utility of patients without complications was dependent on patient and intervention characteristics using regression formulas.[17] The utility was corrected for events using utility multipliers derived from the literature for a specific time duration after the event based on literature or assumptions (Table 2). Even when patients did not experience events, their utility changed over time due to ageing. During the first six years after the intervention, utility

was calculated using a regression formula including time-dependent variables.[17] Beyond year six, yearly absolute disutilities of the general population (males: 0.00128; females: 0.00171) were subtracted from the predicted utility.[19]

Tissue-engineered heart valves

Exact costs and performance of TEHV are unclear, because TEHV are not yet in clinical use. Therefore, we made the following assumptions on TEHV performance. We assumed that safety will be established before TEHV are introduced in clinical practice. For this reason we did not include higher risks of early mortality or valve-related events. The procedure to implant TEHV is expected to be comparable to implanting bioprostheses. Hence, we assumed that early mortality and event risks, which are mainly procedure-related and not valve-related, are comparable for TEHV and bioprostheses with SAVR or TAVI. Further, we assumed that probabilities to die or undergo re-intervention after early and late events were comparable to bioprostheses. To assess long-term performance of TEHV, three aspects of their potential benefits were considered important: (1) Improved *durability* due to lower rates of prosthetic valve dysfunction resulting in longer time to re-intervention; (2) Reduced *thrombogenicity*, the tendency of heart valve substitutes in contact with blood to produce a thrombus or clot, resulting in lower rates of prosthetic valve thrombosis and reduced need for anticoagulation treatment; (3) Improved *infection resistance* resulting in lower rates of endocarditis and subsequent hospitalization and/or re-intervention.

Analyses

Cost-effectiveness analyses were performed from a societal perspective applying a lifetime horizon with costs expressed in 2016 Euros and effects in QALYs. Future health benefits and costs were discounted with 1.5% and 4%, respectively, according to Dutch HTA guidelines.[20]

Several scenario analyses were performed to estimate the impact of variations in TEHV performance on costs, effects, and cost-effectiveness assuming that the price of TEHV is equal to that of bioprostheses (SAVR: €2,500; TAVI: €18,000). First, we performed scenario analyses where durability, thrombogenicity, and infection resistance were varied separately with varying rates compared to bioprostheses. Further, three scenario analyses where performance components of TEHV were varied simultaneously were performed. In the first combined scenario, we assumed '*perfect performance*' of TEHV in which the occurrence of prosthetic valve-related events was equal to the level in the general population (i.e. zero). In the second combined scenario, we assumed *'improved performance*' of TEHV in which the occurrence of prosthetic-valve related events was reduced with 50% compared to bioprostheses. In the final combined scenario, '*partial improved performance*' of TEHV in which the occurrence of events related to

thrombogenicity and infection resistance was reduced with 50%, but prosthetic valve dysfunction increased with 50% due to shorter durability than bioprostheses. In addition, subgroup analyses were performed for patients aged 70-80 and >80 years for the 'improved performance' scenario. In all scenarios, occurrence rates of strokes and bleedings were not varied because these events are influenced by anticoagulation treatment which is only prescribed for patients after aortic valve implantation with bioprostheses during the first three months after the intervention and is likely to be prescribed for TEHV as well.(3) TEHV were compared to bioprostheses implanted using the same approach: either surgical (SAVR) or transcatheter (TAVI) implantation. In the remainder, SAVR and TAVI refers to the comparator treatment, i.e. heart valve implantations with currently used bioprostheses. For all scenarios, we calculated incremental costs, effects and cost-effectiveness ratio (ICER).

Probabilistic sensitivity analysis (PSA) was performed for the 'improved performance' scenario, the most realistic scenario of the scenarios defined above according to experts. PSA was implemented as a double loop: an inner loop, in which 500 patients were sampled with replacement, and an outer loop in which 500 sets of input parameters values of the model were randomly drawn (Supplement 3). For each set of coefficients, mean outcomes over all patients were recorded and the mean and credible interval (i.e. 2.5% and 97.5% percentiles) over all 500 mean values for each outcome were calculated. The incremental costs and effects of TEHV compared to existing heart valves were plotted in cost-effectiveness planes and probabilities that the intervention was cost-effective at certain cost-per-QALY thresholds were displayed in cost-effectiveness acceptability curves (CEAC).

Additionally, the headroom was calculated, which is the maximum costs of TEHV to remain cost-effective compared to bioprostheses when applying a cost-per-QALY threshold (SAVR: €20,000; TAVI: €50,000). Different thresholds for SAVR and TAVI were applied, because in the Netherlands this threshold depends on disease burden with current standard of care; the higher the disease burden, the higher the cost-per-QALY threshold.[23] Disease burden was expressed in proportional shortfall (i.e. fraction of QALYs that people lose relative to their remaining life expectancy when untreated) which can take a value between 0 (minimal burden of disease) and 1 (maximum burden of disease) and was calculated with the iMTA Disease Burden Calculator.[24,25]. The disease burden was 0.19 in SAVR and 0.48 in TAVI patients.

Budget impact reflects the difference in total population-level costs of SAVR or TAVI with bioprostheses compared to TEHV. Budget impact analyses were performed for the 'improved performance' scenario for the first 10 years after introduction of TEHV. Differences in population-level costs were calculated by multiplying the differential

total costs per patient with the expected number of TEHV candidates, assuming substitution rates of 25%, 50%, 75% or 100% of bioprostheses by TEHV. The expected annual number of SAVR patients was 1,931 patients, based on the average annual number of SAVR recorded in the ACSD between 2007-2015. The expected annual number of TAVI patients was 809 or 3,745 patients, based on the average annual number of TAVIs recorded in the Dutch health insurance claims database in 2013 and estimations of Durko et al, respectively.[11, 21]

Validation

Extensive internal validation was performed to check the model's performance using the TECH-VER checklist.[22] External validation was conducted comparing survival and time-to-events derived from our model (applying US survival tables for background mortality [23]) with an external dataset from the US Providence Health System [24] in four subgroups: males and females between 70-80 years old and males and females >80 years old. This Portland dataset contains 2,814 patients aged ≥70 years who underwent SAVR with bioprostheses with 17,525 follow-up years (mean 6.2 years). We did not have access to an external dataset to validate TAVI outcomes.

Table 1. Clinical input parameters

	SAVR	Distribution	Source	TAVI	Distribution	Source
Early mortality, %						
After initial intervention	3.9*	Multivariate normal[7]	ACSD	5.4	Beta (α 65, β 1135)	[25]
After re-intervention	9.0*	Multivariate normal[7]	ACSD	8.6[3]	Uniform (-/+ 10%)	[26]
Early events, %						
Stroke	2.5*	Multivariate normal[7]	ACSD	2.9	Beta (α 58, β 1919)	[25]
Myocardial infarction	1.6*	Multivariate normal[7]	ACSD	1.0	Beta (α 20 , β 1983)	[25]
Vascular complications	-	-		8.1	Beta (α 50, β 565)	[25]
Bleeding[1]	4.2	Beta (α 77, β 1761)	[5]	8.7	Beta (α 11, β 115)	[25]
Arrhythmias/atrial fibrillation	41.5*	Multivariate normal[7]	ACSD	11.0	Beta (α 31, β 249)	[25]
Pacemaker implantation (PI)	8.1	Beta (α 4, β 48)	[5]	12.2	Beta (α 85, β 610)	[25]
Renal failure/acute kidney injury	3.4*	Multivariate normal[7]	ACSD	4.5	Beta (α 10, β 215)	[25]
Prosthetic valve dysfunction[2]	-	-	Assumption	6.8	Beta (α 30, β 405)	[25]
Prosthetic valve thrombosis	-	-	Assumption	-	-	Assumption
Prosthetic valve endocarditis	-	-	Assumption	-	-	Assumption
Late events, %/year ± SD						
Stroke	0.77 ± 0.28	Lognormal	[5]	0.96 ± 0.10[4]	Lognormal	[5]; [27]
Probability of dying (%)	44.0	Beta (α 11, β 14)	[5]	44.0	Beta (α 11, β 14)	[5]
Bleeding	0.75 ± 0.16	Lognormal	[5]	0.95 ± 0.35[4]	Lognormal	[5]; [27]
Probability of dying (%)	39.1	Beta (α 18, β 28)	[5]	39.1	Beta (α 18, β 28)	[5]
Structural valve deterioration	Rate: 0.003 ± 0.001; Shape: 0.124 ± 0.024	Gompertz	[5]	mean log 2.711 ± 0.379; SD log 0.613 ± 0.335	Lognormal	[4]
Probability of dying (%)	17.0	Dirichlet[6] (α^1 18, α^2 45, α^3 41)	[28]	17.0	Dirichlet[6] (α^1 18, α^2 45, α^3 41)	[28]
Probability of re-intervention (%)	43.3		[5]	25.0		[4]
Probability TAVI	6.2	Uniform (6.1-6.3)	[21]	100	Assumption	
Probability SAVR	93.8		[21]	0	Assumption	

Table 1. Continued

	SAVR	Distribution	Source	TAVI	Distribution	Source
Probability conservative treatment	39.7			58.0	Assumption	
Probability TAVI	61.7	Uniform (42.0-81.7)	[21]	0	Assumption	
Probability medical treatment	38.3		[21]	100	Assumption	
Non-structural valve dysfunction	0.47 ± 0.27	Lognormal	[5]	-	Assumption	
Probability of dying (%)	5.0	Dirichlet[6] (α^1 1, α^2 10, α^3 15)	[28]	-	-	
Probability of re-intervention (%)	38.5		[5]	-		
Prosthetic valve thrombosis	0.12 ± 0.09	Lognormal	[5]	0.24[5]	Uniform (-/+ 20%)	[29]
Probability of dying (%)	0.0	Dirichlet[6] (α^1 0, α^2 2, α^3 15)	[28]	0.0	Dirichlet[6] (α^1 0, α^2 3, α^3 23)	[28]
Probability of re-ntervention (%)	0.12		[30]	0.12		[31]
Prosthetic valve endocarditis	0.57 ± 0.08	Lognormal	[5]	0.54 ± 0.10	Lognormal	[25]
Probability of dying (%)	34.0	Dirichlet[6] (α^1 26, α^2 37, α^3 13)	[28]	34.0	Dirichlet[6] (α^1 26, α^2 37, α^3 13)	[28]
Probability of re-intervention (%)	49.0		[5]	49.0		[5]
Hazard ratio excess mortality	0.86	Uniform (-/+ 10%)	[5]	1.40	Uniform (-/+ 10%)	This study

SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve implantation. ACSD: Adult Cardiac Surgery Database. [1]Definition of bleeding is reexploration for bleeding after SAVR and major bleedings after TAVI. [2]Paravalvular leak after TAVI. [3]Hazard ratio of 1.6 applied to early mortality risk of initial intervention. [4]Hazard ratio of SAVR patients compared to the general population applied to occurrence in age and sex matched general population for the TAVI population. [5]Blackstone & Kirklin have shown that valve thrombosis mainly occurs during the first year after surgical mechanical aortic valve implantation and deteriorates to almost zero after six years.[32] The higher occurrence in the early phase may be caused by suboptimal anticoagulation treatment in the first postintervention period. Since, the mean follow-up of the Bern TAVI Registry was only one year, it is likely that the occurrence rate of valve thrombosis after TAVI found in this study will not remain constant but will reduce over time. Therefore we recalculated the linearized occurrence rate of 0.69%/year, assuming that it will be zero from year 7 onwards. [6]Dirichlet distribution parameters: α1 = number of deaths, α2 = number of re-interventions, α3 = number of other treatment. [7]Multivariate normal distribution: coefficients of the regression model are randomly drawn from a multivariate normal distribution based on coefficients and variance-covariance matrix.

Table 2. Costs and utilities

		Distribution	Source
Intervention costs			
SAVR	25,474	Multivariate normal[4]	[11]*
TAVI	33,178	Multivariate normal[4]	[11]*
Event treatment costs			
Stroke	3,054	Multivariate normal[4]	[11]*
Myocardial infarction	5,157	Multivariate normal[4]	[11]*
Vascular complications	5,112	Uniform (-/+ 20%)	[33]
Reexploration for bleeding	5,048	Uniform (-/+ 20%)	[33]
Bleeding	1,617	Uniform (-/+ 20%)	[33]
Atrial fibrillation (without PI)	1,225	Multivariate normal[4]	[11]*
Pacemaker implantation (PI)	11,738	Multivariate normal[4]	[11]*
Acute kidney injury/renal failure	9,650	Multivariate normal[4]	[11]*
Prosthetic valve dysfunction	1,478	Uniform (-/+ 20%)	[34-39]
Prosthetic valve thrombosis	5,824	Uniform (-/+ 20%)	[38-40]
Prosthetic valve endocarditis	8,923	Multivariate normal[4]	[11]*
Re-intervention SAVR	25,936	Multivariate normal[4]	[11]*
Re-intervention TAVI	33,178	Multivariate normal[4]	[11]*
Other healthcare cost[1]			
Postintervention year 1	18,479		[11]*
Postintervention year 2	10,607	Multivariate normal[4]	[11]*
Postintervention year 3	10,832		[11]*
Productivity costs of unpaid work[3]	**Costs per month**		
SAVR	44	Multivariate normal[4]	[17]
TAVI	50	Multivariate normal[4]	[17]
Informal care costs[3]	**Costs per month**		
SAVR	164	Multivariate normal[4]	[17]
TAVI	388	Multivariate normal[4]	[17]
Utilities at start of the simulation			
SAVR	0.837	Multivariate normal[4]	[17]
TAVI	0.718	Multivariate normal[4]	[17]

Table 2. Continued

			Distribution	Source
Utilities after events	**Utility multiplier**	**Duration**		
Stroke	0.841	Lifetime	Uniform[3]	[41, 42]
Myocardial infarction	0.914	1 year	Uniform[3]	[43, 44]
Vascular complications	0.981	1 week	Uniform[3]	[45]
Bleeding	0.965	1 year	Uniform[3]	[46]
Atrial fibrillation (without PI)	0.955	1 year	Uniform[3]	[47]
Pacemaker implantation (PI)	0.804	1 month	Uniform[3]	[48]
Acute kidney injury/renal failure	0.804	1 year	Uniform[3]	[49]
Re-intervention	0.946	SAVR/TAVI: 4/1 month(s)	Uniform[3]	[50]/[5]
Conservative treatment of:				
Prosthetic valve dysfunction	0.886[2]	Lifetime	Uniform[3]	[35, 51]
Prosthetic valve thrombosis	0.968[2]	10 days	Uniform[3]	[40, 52]
Prosthetic valve endocarditis	0.968[2]	6 weeks	Uniform[3]	[52, 53]

SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve implantation. *Mean in the Vektis database adjusted to 2016€. Costs in the model dependent on patient and intervention characteristics using (M)GLM. [11] [1]Mean total healthcare costs per year including costs of treatment of events and death (costs types are estimated separately in the model), but excluding intervention costs. Costs are based on data of SAVR patients, but it is assumed they are also applicable to TAVI patients. [2]Conservative treatment, no re-intervention. [3]Mean across all patients, including patients without unpaid work or informal care. 350% deviation of 1-utility multiplier to prevent the utility multiplier from exceeding 1. [4]Multivariate normal distribution: coefficients of the regression model are randomly drawn from a multivariate normal distribution based on coefficients and variance-covariance matrix.

RESULTS

Results of the scenario analyses are presented in Table 3. Of the three TEHV performance components, durability had the highest impact on cost-effectiveness. This is emphasized by the results of the 'partial improved scenario' where the consequences of reductions in durability of TEHV for the cost-effectiveness could not be offset by reductions in thrombogenicity and improvements in infection resistance of TEHV. The 'perfect performance' scenario provides insight in the maximum lifetime QALY gain and cost savings of TEHV compared to bioprostheses: 0.249 QALYs and €1,344 per SAVR patient and 0.079 QALYs and €789 per TAVI patient. In the 'improved performance' scenario, lifetime QALY gains and cost reductions of TEHV versus bioprostheses were 0.131 QALY and €639 per SAVR patient and 0.043 QALY and €368 per TAVI patient, which translates to headrooms (i.e. the maximum additional costs above the price of a bioprosthesis) of €3,255 and €2,498 for surgical and transcatheter TEHV, respectively. The median SVD-free life expectancy increased from 9.4 after SAVR to 10.0 years with TEHV and from 4.6 after TAVI to 4.7 years with TEHV (Table S13). Subgroup analyses showed that QALY gain was higher in patients 70-80 years than in patients >80 years old, while cost reductions were comparable.

In the PSA of the 'improved performance' scenario, incremental costs and effects varied as shown in the cost-effectiveness plane (Figure 2a), with most data points lying in the south-east quadrant, suggesting QALY gains at lower costs. The CEACs show that when applying the appropriate cost-per-QALY threshold (SAVR €20,000; TAVI €50,000), there is a probability of cost-effectiveness of 100% or 99% for TEHV versus bioprostheses in SAVR or TAVI patients, respectively (Figure 2b).

Figure 3 (Table S14) shows that implementing SAVR and TAVI with TEHV instead of bioprostheses resulted in cost savings of the Dutch healthcare budget in the next 10 years varying between €2.8 and €11.2 million (SAVR) and €3.2 and €12.8 million (TAVI), for 25% or 100% substitution of bioprostheses by TEHV.
The headroom (i.e. the maximum additional costs above the price of a bioprosthesis) varied from €38 (SAVR) and €35 (TAVI) if TEHV would only result in a small reduction in thrombogenicity to €6,322 (SAVR) and €4,734 (TAVI) if there would be no prosthetic valve-related events at all using TEHV (Table 3).

Extensive internal validation was performed to check the model's performance using the TECH-VER checklist.[22] Further, Kaplan-Meier curves of survival and time to SVD that were used as input were comparable to curves derived from the model (Figures S2-3).[5] External validation of the model's survival output with the Portland dataset showed that results were comparable, but the model predicted a slightly higher survival, especially in females

between 70-80 years old (Figure S4). There were discrepancies between cumulative incidence functions of events; the number of events observed in Portland were lower than in the simulation (Figures S5-9).

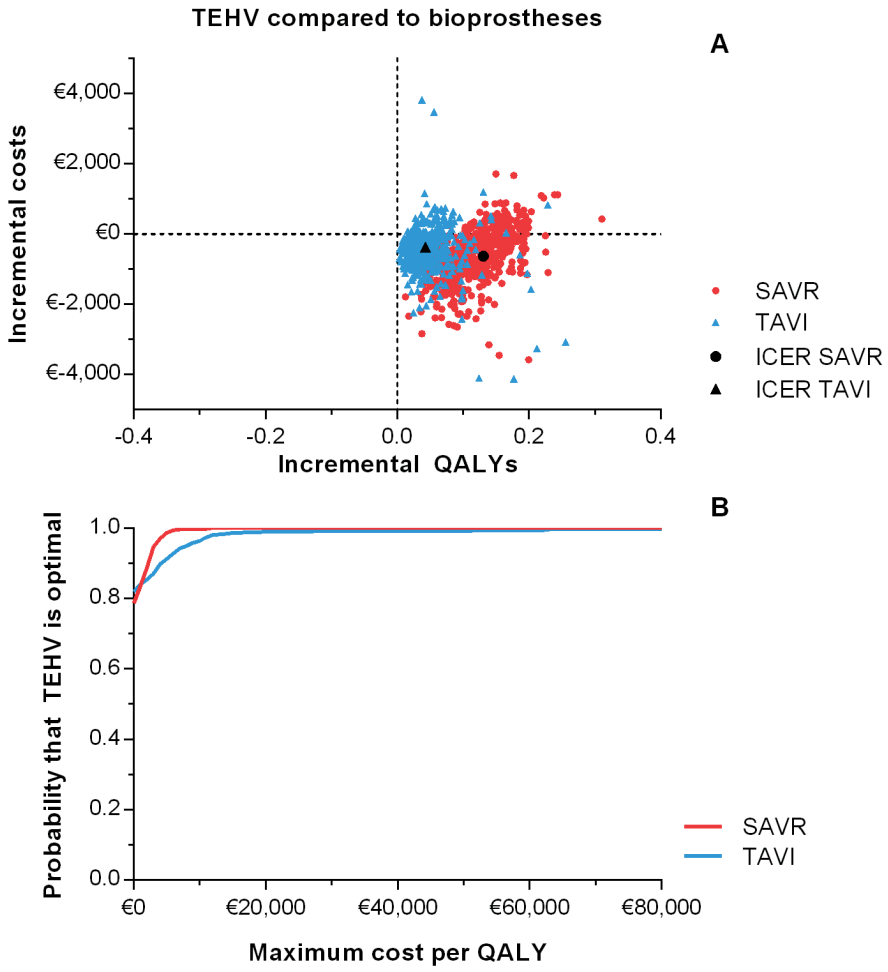


Figure 2. Probabilistic sensitivity analyses outcomes of surgical (SAVR) and transcatheter (TAVI) aortic valve implantation with TEHV (50% improved performance compared to currently used heart valve prostheses) compared to bioprostheses. A: Cost-effectiveness plane. B: Cost-effectiveness acceptability curve (CEAC)

Table 3. Cost-effectiveness results of scenario analyses

	LY	QALYs	Societal costs	Healthcare costs	ΔLYs	ΔQALYs	ΔSocietal costs	ΔHealthcare costs	ICER	Headroom (Cost/QALY threshold €20,000;50,000)
SAVR										
SAVR with existing valve prostheses	10.196	6.761	150,860	137,447						
- Subgroup patients aged 70-80 years	11.047	7.358	159,939	145,852						
- Subgroup patients aged >80 years	6.985	4.488	114,759	103,814						
Improved durability of TEHV										
No prosthetic valve dysfunction events	10.348	6.890	149,440	136,813	0.152	0.129	-1,420	-634	-	4,004
75% less prosthetic valve dysfunction events	10.317	6.861	149,780	136,994	0.121	0.101	-1,080	-453	-	3,094
50% less prosthetic valve dysfunction events	10.280	6.830	150,105	137,132	0.084	0.069	-756	-315	-	2,134
25% less prosthetic valve dysfunction events	10.245	6.800	150,522	137,329	0.049	0.040	-338	-118	-	1,130
Reduced thrombogenicity of TEHV										
No valve thrombosis events	10.196	6.761	150,758	137,369	0.001	0.000	-102	-79	-	110
75% less valve thrombosis events	10.196	6.761	150,792	137,395	0.000	0.000	-69	-53	-	75
50% less valve thrombosis events	10.196	6.761	150,816	137,414	0.000	0.000	-44	-33	-	50
25% less valve thrombosis events	10.196	6.761	150,827	137,421	0.000	0.000	-34	-26	-	38
Improved infection resistance of TEHV										
No endocarditis events	10.361	6.877	151,118	137,938	0.165	0.116	257	491	2,222	2,061
75% less endocarditis events	10.323	6.850	151,109	137,865	0.127	0.089	248	418	2,792	1,530
50% less endocarditis events	10.283	6.821	151,030	137,729	0.087	0.061	170	282	2,797	1,044
25% less endocarditis events	10.235	6.788	150,889	137,530	0.039	0.028	28	83	1,028	526
Perfect TEHV (no prosthetic-valve related events)	10.516	7.010	149,517	137,219	0.320	0.249	-1,344	-228	-	6,322
Improved TEHV (50% less prosthetic valve-related events)	10.368	6.892	150,221	137,383	0.172	0.131	-639	-65	-	3,255
- Subgroup patients aged 70-80 years	11.248	7.512	159,397	145,968	0.201	0.154	-542	115	-	3,616
- Subgroup patients aged >80 years	7.065	4.545	114,161	103,436	0.079	0.057	-598	-378	-	1,740
Decreased durability (50% more events) but reduced thrombogenicity and improved infection resistance (50% less events)	10.220	6.814	152,278	138,452	0.024	0.053	1,417	1,005	26,841	-361

Table 3. Continued

	LY	QALYs	Societal costs	Healthcare costs	ΔLYs	ΔQALYs	ΔSocietal costs	ΔHealthcare costs	ICER	Headroom (Cost/QALY threshold €20,000;50,000)
TAVI										
TAVI with existing valve prostheses	5.679	3.134	100,243	81,202						
- Subgroup patients aged 70-80 years	8.000	4.089	120,195	94,010						
- Subgroup patients aged >80 years	4.435	2.630	89,888	74,626						
Improved durability of TEHV										
No prosthetic valve dysfunction events	5.754	3.182	99,665	80,616	0.074	0.048	-578	-586	-	1,540; 2,983
75% less prosthetic valve dysfunction events	5.739	3.172	99,834	80,771	0.060	0.039	-410	-430	-	1,180; 2,335
50% less prosthetic valve dysfunction events	5.721	3.160	99,970	80,902	0.042	0.027	-273	-300	-	807; 1,608
25% less prosthetic valve dysfunction events	5.702	3.148	100,104	81,045	0.023	0.014	-139	-156	-	423; 849
Reduced thrombogenicity of TEHV										
No valve thrombosis events	5.680	3.134	100,121	81,092	0.000	0.000	-122	-110	-	126; 132
75% less valve thrombosis events	5.680	3.134	100,156	81,123	0.000	0.000	-87	-79	-	91; 97
50% less valve thrombosis events	5.680	3.134	100,180	81,145	0.000	0.000	-64	-57	-	66; 69
25% less valve thrombosis events	5.679	3.134	100,208	81,170	0.000	0.000	-35	-31	-	35; 35
Improved infection resistance of TEHV										
No endocarditis events	5.742	3.164	100,179	81,074	0.063	0.030	-64	-128	-	668; 1574
75% less endocarditis events	5.729	3.157	100,217	81,121	0.050	0.024	-26	-81	-	502; 1216
50% less endocarditis events	5.713	3.149	100,218	81,146	0.033	0.016	-25	-55	-	341; 815
25% less endocarditis events	5.692	3.140	100,205	81,155	0.013	0.006	-38	-47	-	166; 358
Perfect TEHV (no prosthetic valve-related events)	5.817	3.213	99,454	80,366	0.137	0.079	-789	-836	-	2,367; 4,734
Improved TEHV (50% less prosthetic valve-related events)	5.755	3.176	99,875	80,786	0.075	0.043	-368	-416	-	1,220; 2,498
- Subgroup patients aged 70-80 years	8.156	4.174	119,825	93,526	0.156	0.086	-370	-485	-	2,082; 4,650
- Subgroup patients aged >80 years	4.474	2.652	89,557	74,261	0.038	0.023	-331	-365	-	783; 1,461
Decreased durability (50% more events) but reduced thrombogenicity and improved infection resistance (50% less events)	5.666	3.139	100,904	81,586	-0.014	0.005	660	385	122,276; 71,225	-552; -390

'-' TEHV dominates. LY: life years. QALY: quality adjusted life years. ICER: incremental cost-effectiveness ratio. WTP: willingness to pay per QALY gained in Euros. SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve implantation. TEHV: tissue-engineered heart valves.

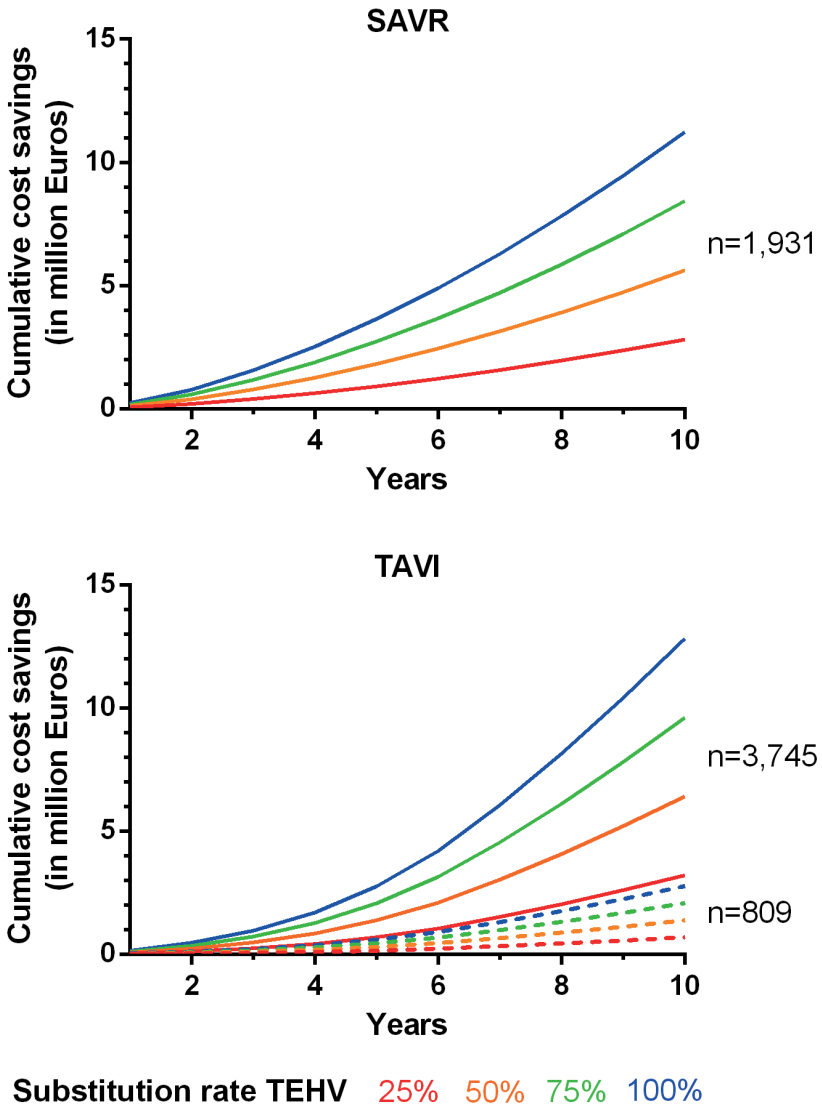


Figure 3. Cumulative cost savings in the first 10 years after introduction of surgical (SAVR; left) and transcatheter (TAVI; right) aortic valve implantation with TEHV ('improved performance' scenario) compared to bioprostheses.

DISCUSSION

This early HTA study showed that TEHV are likely to be cost-effective when used in the most frequent indication for heart valve surgery in the patient group with the highest prevalence of this type of heart valve disease, namely elderly patients with aortic valve disease.[2] Improvements in durability of TEHV had the greatest impact on cost-effectiveness. Improved durability not only increased lifetime QALYs, but also reduced costs. In addition, it is worthwhile to pursue improved resistance to infection, considering the lifetime QALY gains that can be achieved with acceptable costs when prosthetic valve endocarditis is prevented. Reductions in thrombogenicity are unlikely to significantly impact cost-effectiveness of TEHV in elderly patients. In these patients, reduced thrombogenicity only reduces valve thrombosis occurrence, since lifelong anticoagulation treatment is not required with bioprostheses or patients already use anticoagulation treatment for other indications (resulting in less strokes and more bleedings than in the general population).[5] However, reduced thrombogenicity may have more impact on cost-effectiveness of TEHV in younger patients who are eligible for mechanical valves and often have no other indication for anticoagulation treatment as reduced thrombogenicity would not only reduce valve thrombosis and strokes, but also the need of lifelong anticoagulation associated with increased bleedings. Finally, subgroup analyses showed that benefits of TEHV are lower in older patients (>80 years), because their lifetime risks on events and subsequent re-intervention are lower due to their shorter life expectancy.

In the Netherlands, using TEHV instead of bioprostheses in elderly patients may lead to costs savings of more than €10 million in the next decade. However, the magnitude of cost savings depends on the perspective and the substitution rate of TEHV. From a healthcare payer perspective, the cost savings of the introduction of TEHV would be smaller compared to SAVR and even larger compared to TAVI than from a societal perspective. Furthermore, although TEHV may eventually become the gold standard heart valve substitute, it is more likely that substitution will increase gradually, as observed in the adoption of TAVI in western Europe where four years after introduction only 17.9% of potential candidates underwent TAVI.[54] Finally, the actual cost savings might be higher than reported in this study, because our estimates were not adjusted for the expected increase in aortic valve implantations due to ageing of the general population.[2, 6]

We assumed that prices of TEHV and bioprostheses were equal. However, considering the QALY gains TEHV might achieve, TEHV may be sold at a higher price and still remain cost-effective compared to bioprostheses. Depending on TEHV performance, the headroom varied between €38-€6,323 per surgical TEHV and €35-€4,734 per transcatheter TEHV. When

we would also apply a cost-per-QALY threshold of €20.000 for transcatheter TEHV, the headroom varied between €35-€2,367 per transcatheter TEHV.

External validation of model outcomes with actual survival and event data from the Providence Health System showed that the model predicted a slightly higher survival. Possible explanations can be the slightly younger mean age and considerably lower concomitant CABG proportion in patients in the simulation compared to the Portland dataset (Table S15). Survival difference was larger in females between 70-80 years old than in other subgroups. This can be explained by higher survival of females than males in the general population applied in the model, while survival of males and females between 70-80 years old in the Portland dataset were comparable. Further, cumulative incidence of valve-related events was higher in the model than in the Portland dataset. Explanations for this discrepancy may be underreporting of events, too short follow-up of patients because mean event-free life expectancy in the model was higher than mean follow-up of patients in the Portland dataset, or differences in outcomes between the Netherlands and the US.

This study has several limitations. Firstly, relationships between occurrence rates of valve-related events after aortic valve implantation on the one hand and patient and intervention characteristics and history of previous valve-related events on the other hand remain poorly defined and could, thus, not be incorporated into our model. Secondly, the model requires assumptions about evolution of event occurrence rates and hazard ratio for excess mortality beyond the observed follow-up period, which introduced uncertainty in the extrapolation of these events. Thirdly, most healthcare cost estimates were based on health insurances claims data which means that, conflicting with the applied societal perspective, costs represent expenditures reimbursed by health insurers based on agreements between healthcare providers and insurers, not actual costs. Fourthly, this study was performed from a Dutch perspective and may therefore not be generalizable to countries with other health care systems. Finally, due to limited data availability, additional informal care use or productivity loss after events, except for stroke and re-intervention, were not incorporated. However, additional informal care use and productivity loss of patients after hospitalization for these events are probably relatively low and therefore will not have a large impact on total costs.

The results of this study can be useful for different stakeholders. First, we informed biomedical developers about minimum performance requirements and maximum additional costs of TEHV to be cost-effective compared to currently used bioprostheses early in the development process.[55] We showed that developers should primarily focus on durability, even in elderly patients. In addition, it can be worthwhile to pursue

improving infection resistance considering the high impact on QALYs. Reductions in thrombogenicity did not have a large impact on cost-effectiveness in this patient group, but are expected to have more benefits in younger patients eligible for mechanical valve substitutes. Further, a higher price for TEHV than bioprostheses is possible, even if there are only small improvements in performance. Second, it provides patients and clinicians the first estimates of potential improvements in clinical outcomes of TEHV. Providing clinicians information about possible future treatment options may result in faster adoption of TEHV in clinical practice.[56] We showed that although the benefits of TEHV are relatively low in elderly patients due to their limited remaining life expectancy, TEHV can result in improvements in (quality-adjusted) life expectancy and reduced costs. Finally, this study informs Dutch healthcare payers about the possible entrance of TEHV to the market and its associated national cost savings, which may result in more timely decisions about reimbursement.[56] In conclusion, despite the relatively short life expectancy of elderly patients undergoing aortic valve implantation, the potential cost-effectiveness of TEHV in the aortic position in elderly patients is promising.

Funding. This work was supported by the Netherlands Cardio Vascular Research Initiative: The Dutch Heart Foundation, Dutch Federation of University Medical Centers, the Netherlands Organization for Health Research and Development and the Royal Netherlands Academy of Sciences.

Conflicts of interest. None.

REFERENCES

1. Iung, B., et al., *A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease.* European Heart Journal, 2003. 24(13): p. 1231-1243.
2. Nkomo, V.T., et al., *Burden of valvular heart diseases: a population-based study.* The Lancet, 2006. **368**(9540): p. 1005-1011.
3. Baumgartner, H., et al., *2017 ESC/EACTS Guidelines for the management of valvular heart disease.* European heart journal, 2017. **38**(36): p. 2739-2791.
4. Sokoloff, A., et al., *Long-term assessment of durability of transcatheter aortic valves. Experience from the pioneer center.* Archives of Cardiovascular Diseases Supplements, 2018. **10**(1): p. 72.
5. Huygens, S.A., et al. *Outcomes after aortic valve replacement with bioprostheses in elderly patients: systematic review, meta-analysis, and patient level simulation*. in *Heart Valve Society 4th Annual Meeting*. 2018. New York.
6. Yacoub, M.H. and J.J.M. Takkenberg, *Will heart valve tissue engineering change the world?* Nat Clin Pract Cardiovasc Med, 2005. **2**(2): p. 60-61.
7. Wissing, T.B., et al., *Biomaterial-driven in situ cardiovascular tissue engineering—a multi-disciplinary perspective.* NPJ Regenerative medicine, 2017. **2**(1): p. 18.
8. Kluin, J., et al., *In situ heart valve tissue engineering using a bioresorbable elastomeric implant–From material design to 12 months follow-up in sheep.* Biomaterials, 2017. **125**: p. 101-117.
9. Bouten, C.V., A. Smits, and F. Baaijens, *Can we grow valves inside the heart? perspective on material-based in situ heart valve tissue engineering.* Frontiers in Cardiovascular Medicine, 2018. **5**: p. 54.
10. Bockeria, L.C., Thierry; Kim, Alex; Shatalov, Konstantin; Makarenko, Vladimir; Cox, Martijn; Svanidze, Oleg. *Polymeric bioabsorbable vascular graft in modified Fontan procedure - two-year follow-up*. in *7th World Congress of Pediatric Cardiology & Cardiac Surgery (WCPCCS)*. 2017. Barcelona.
11. Huygens, S.A., et al., *How much does a heart valve implantation cost and what are the health care costs afterwards?* Open Heart, 2018. **5**(1).
12. Huygens, S.A., et al., *Conceptual model for early health technology assessment of current and novel heart valve interventions.* Open Heart, 2016. **3**(2): p. e000500.
13. Centraal Bureau voor de Statistiek (CBS). *Overlevingskansen; geslacht, leeftijd*. 2016 3-8-2017 [cited 2017 18-1-2018]; Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70701ned/table?ts=1517913558300.
14. Kvidal, P., et al., *Observed and relative survival after aortic valve replacement.* Journal of the American College of Cardiology, 2000. **35**(3): p. 747-756.
15. Eggebrecht, H. and R.H. Mehta, *Transcatheter aortic valve implantation (TAVI) in Germany 2008-2014: on its way to standard therapy for aortic valve stenosis in the elderly?* EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology, 2015. **11**(5).

16. Organisation for Economic Co-operation and Development (OECD). *Expenditure by disease, age and gender under the System of Health Accounts (SHA) Framework : Current health spending by age*. 2011 [cited 2017.
17. Huygens, S.A., et al., *Beyond the clinical impact of heart valve implantations - health-related quality of life, informal care, and productivity.* Submitted, 2018.
18. Van Eeden, M., et al., *The burden of stroke in the Netherlands: estimating quality of life and costs for 1 year poststroke.* BMJ open, 2015. **5**(11): p. e008220.
19. Versteegh, M.M., et al., *Dutch tariff for the five-level version of EQ-5D.* Value in health, 2016.
20. Zorginstituut, N., *Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg.* Diemen: Zorginstituut Nederland, 2015.
21. Durko, A.P., et al., *Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections.* European heart journal, 2018.
22. Buyukkaramikli N.C, R.-v.M.M.P., Severens J.L.H, Al M. , *TECH-VER CHECKLIST: a quality assurance and verification checklist for the technical implementation of health economic decision analytic models*. 2016, iMTA, Rotterdam, the Netherlands.
23. Arias, E., *United States Life Tables, 2004.* National Vital Statistics Reports, 2007. **56**(9): p. 40.
24. Eddy, D.M., et al., *Model Transparency and Validation A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force–7.* Medical Decision Making, 2012. **32**(5): p. 733-743.
25. Gargiulo, G., et al., *Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement: A Systematic Review and Meta-analysis.* Annals of Internal Medicine, 2016. **165**(5): p. 334-344.
26. Makkar, R.R., et al., *Determinants and outcomes of acute transcatheter valve-in-valve therapy or embolization: a study of multiple valve implants in the US PARTNER trial (Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve).* Journal of the American College of Cardiology, 2013. **62**(5): p. 418-430.
27. Rothwell, P., et al., *Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study).* The Lancet, 2005. **366**(9499): p. 1773-1783.
28. van Geldorp, M.W.A., et al., *Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk.* J Thorac Cardiovasc Surg, 2009. **137**(4): p. 881-886. e5.
29. Franzone, A., et al., *Transcatheter aortic valve thrombosis: incidence, clinical presentation and long-term outcomes.* European Heart Journal-Cardiovascular Imaging, 2018. **19**: p. 398–404.
30. Jander, N., et al., *The porcine valve type predicts obstructive thrombosis beyond the first three postoperative months in bioprostheses in the aortic position.* International journal of cardiology, 2015. **199**: p. 90-95.
31. Latib, A., et al., *Treatment and clinical outcomes of transcatheter heart valve thrombosis.* Circulation: Cardiovascular Interventions, 2015. **8**(4): p. e001779.
32. Blackstone, E.H. and J.W. Kirklin, *Death and other time-related events after valve replacement.* Circulation, 1985. **72**(4): p. 753-767.

33. Geisler, B.P., et al., *Cost-effectiveness and projected survival of self-expanding transcatheter versus surgical aortic valve replacement for high risk patients in a european setting. a dutch analysis based on the Corevalve high-risk trial.* Structural Heart, 2017(just-accepted).
34. van Vliet, M., et al., *Trends in admission prevalence, illness severity and survival of haematological patients treated in Dutch intensive care units.* Intensive care medicine, 2014. **40**(9): p. 1275-1284.
35. van der Pol, S., et al., *An Economic Evaluation of Sacubitril/Valsartan for Heart Failure Patients in the Netherlands.* Value in Health, 2017. **20**(3): p. 388-396.
36. Packer, M., et al., *Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure.* Circulation, 2014: p. CIRCULATIONAHA. 114.013748.
37. McMurray, J.J.V., et al., *Angiotensin–neprilysin inhibition versus enalapril in heart failure.* New England Journal of Medicine, 2014. **371**(11): p. 993-1004.
38. Zorginstituut Nederland. *Medicijnkosten.* 2017 October 2, 2017]; Available from: http://www.medicijnkosten.nl/.
39. Kanters, T.A., et al., *Update of the Dutch manual for costing studies in health care.* PloS one, 2017. **12**(11): p. e0187477.
40. Özkan, M., et al., *Ultraslow thrombolytic therapy: A novel strategy in the management of PROsthetic MEchanical valve Thrombosis and the prEdictors of outcomE: The Ultra-slow PROMETEE trial.* American heart journal, 2015. **170**(2): p. 409-418. e1.
41. Rothwell, P.M., et al., *Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study).* The Lancet, 2004. **363**(9425): p. 1925-1933.
42. Rivero-Arias, O., et al., *Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome.* Medical decision making, 2010. **30**(3): p. 341-354.
43. Reed, S.D., et al., *Resource use, costs, and quality of life among patients in the multinational Valsartan in Acute Myocardial Infarction Trial (VALIANT).* American heart journal, 2005. **150**(2): p. 323-329.
44. Lewis, E.F., et al., *Impact of cardiovascular events on change in quality of life and utilities in patients after myocardial infarction: a VALIANT study (valsartan in acute myocardial infarction).* JACC: Heart Failure, 2014. **2**(2): p. 159-165.
45. Cohen, D.J., et al., *Evaluating the potential cost-effectiveness of stenting as a treatment for symptomatic single-vessel coronary disease. Use of a decision-analytic model.* Circulation, 1994. **89**(4): p. 1859-1874.
46. Amin, A.P., et al., *Impact of bleeding on quality of life in patients on DAPT: insights from TRANSLATE-ACS.* Journal of the American College of Cardiology, 2016. **67**(1): p. 59-65.
47. Berg, J., et al., *Factors determining utility measured with the EQ-5D in patients with atrial fibrillation.* Quality of Life Research, 2010. **19**(3): p. 381-390.
48. van Eck, J.M., et al., *Predictors of improved quality of life 1 year after pacemaker implantation.* American heart journal, 2008. **156**(3): p. 491-497.
49. Nisula, S., et al., *Six-month survival and quality of life of intensive care patients with acute kidney injury.* Critical Care, 2013. **17**(5): p. R250.

50. Kaier, K., et al., *Quality of life among elderly patients undergoing transcatheter or surgical aortic valve replacement–a model-based longitudinal data analysis.* Health and quality of life outcomes, 2016. **14**(1): p. 109.
51. Swedberg, K., et al., *Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study.* The Lancet, 2010. **376**(9744): p. 875-885.
52. Göhler, A., et al., *Utility Estimates for Decision–Analytic Modeling in Chronic Heart Failure—Health States Based on New York Heart Association Classes and Number of Rehospitalizations.* Value in Health, 2009. **12**(1): p. 185-187.
53. Habib, G., et al., *2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM).* European heart journal, 2015. **36**(44): p. 3075-3128.
54. Mylotte, D., et al., *Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization.* Journal of the American College of Cardiology, 2013. **62**(3): p. 210-219.
55. Pietzsch, J.B. and M.E. Paté-Cornell, *Early technology assessment of new medical devices.* International journal of technology assessment in health care, 2008. **24**(01): p. 36-44.
56. Buisman, L.R., et al., *The early bird catches the worm: early cost-effectiveness analysis of new medical tests.* International journal of technology assessment in health care, 2016: p. 1-8.

SUPPLEMENTAL MATERIAL

Supplement 1

To be in line with the definition in the ACSD and published literature, the definition of cerebrovascular accident was changed to stroke for both SAVR and TAVI. In addition, atrial fibrillation and acute kidney injury were changed into arrhythmias and renal failure for SAVR patients to be in line with the definition used in the ACSD. Finally, conversion to another approach (transcatheter to surgical valve implantation and vice versa) was excluded from the final decision analytic model. Emergent conversion from TAVI to SAVR occurs rarely (1.2%-2.1%) and according to expert opinion conversion from SAVR to TAVI occurs even less. [1, 2] In addition, since the causes of conversion of approach are not related to the prosthetic heart valve itself, the conversion rate is likely to be comparable for TEHV and existing heart valve substitutes.[2]

Supplement 2

For estimation of the hazard ratios of the additional excess mortality not directly resulting from valve-related events relative to background mortality, the model containing only background mortality and mortality due to valve-related events (excluding early mortality) was run for 10,000 iterations at the mean age and proportion of males of the UK TAVI registry. [3] Subsequently, the hazard ratios were estimated by fitting the survival output of this simulation model to the survival observed in the UK TAVI registry (excluding early mortality) using varying values for the hazard ratio of excess mortality. The best fit was determined by using the least squares method (Table below).

Table. Least squares regression of modeled survival vs. observed survival for estimation of excess mortality not directly related to valve-related events

Hazard ratio[1]	Sum of squared residuals[2]
0.9	6200
1.0	4141
1.4	268
1.5	**113**
1.6	197
1.7	493
2.0	2341

Bold print indicates the selected model. [1]Hazard ratio of background mortality + excess mortality relative to background mortality. [2]Sum of squared residuals between microsimulation-based survival and survival observed in our meta-analysis of Kaplan-Meier freedom from all-cause mortality.

Supplement 3

To estimate the numbers of patients and simulations required in our probabilistic sensitivity analyses (PSA), we used the approach described in O'Hagan et al. as recommended by the NICE DSU guidelines on patient-level modelling.[4] In this approach the number of PSA runs (outer loop = N) and patients per PSA run (inner loop = n) needed to achieve accurate cost-effectiveness estimates while keeping the number of runs as small as possible can be estimated. The cost-effectiveness measure used in this estimation was the number of undiscounted QALYs.

The box below showed the approximations presented by O'Hagan et al. that we used. According to O'Hagan et al. the approximations are sufficiently accurate when k is at least 25 and c is less than or equal to 0.2.

M = 8k/c2 = N*n
n = 1 + k

N = number of PSA runs (outer loop)
n = number of patients per PSA run (inner loop)
k = patient-level variance / parameter variance
c = coefficient of variance = SD parameter / mean of parameter

The patient-level variance was 27.37, estimated with a deterministic run of 25.000 patients. The parameter variance was 0.30, which was the mean of 500 model runs each of them based on 100 patients. Therefore, k was 27.37 / 0.30 = 92. Based on the formulas described above the number of patients per PSA run would be 92 + 1 = 93 (after rounding up). Assuming a c of 0.2, M = 18,679 and the number of PSA runs would be 200 (after rounding up). However, the choice of c = 0.2 was arbitrary and based on the minimum accuracy requirement and there is no generally accepted threshold value for c in the literature. Therefore, we chose to run the 500 PSA runs including 500 patients each, translating to a value for c of approximately 0.12 (i.e. almost twice more accurate).

Table S1. Baseline characteristics of patient populations

BASELINE CHARACTERISTICS	SAVR (n=15,405)	TAVI (n=809)
Patient related		
Age, mean±SD (range)	77.0±4.1 (71-94)	81.9±4.9 (70-94)
Gender	55.03	47.84
Previous cardiac surgery	7.81	-
Previous valve replacement[1]	-	-
Preoperative serum creatinine level > 200 µmol/l	1.79	-
LV function		
LVEF >50%	77.74	-
LVEF 30-50%	18.42	-
LVEF <30%	3.84	-
COPD	15.29	-
Peripheral vascular disease (PVD)	13.29	-
Neurological dysfunction	2.80	-
Previous CVA[1]	-	-
Preoperative endocarditis	2.06	-
Instable angina pectoris	1.06	-
Pulmonary hypertension	2.99	-
Co-morbidity categories in cost-analyses		
COPD, DM, kidney disease and/or HF	53.04	64.03
Hypertension	31.86	24.60
Other comorbidities	5.90	4.45
No comorbidities	9.20	6.92
Socioeconomic status (SES, in quartiles)		
0-20	23.62	24.97
21-40	25.64	19.90
41-70	26.35	28.18
71-100	24.39	26.95
Procedure related		
Type of valve prosthesis (biological or mechanical)[2]	-	-
Emergency procedure	2.03	-
Concomitant procedures		
CABG	44.48	-
Other valve repair	7.69	
Thoracic aorta surgery	5.84	-
Bentall procedure	1.51	
Aorta ascendens procedure	0.90	-
MAZE	0.40	-
Aortic arch procedure	0.40	-
Aortic root procedure	0.39	-
Aorta descendens procedure	0.08	-
Other valve replacement	0.04	-

Unless stated otherwise, results presented as percentages. SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve implantation. LV: left ventricle. LVEF: left ventricular ejection fraction. COPD: chronic obstructive pulmonary disease. CVA: cerebrovascular accident. DM: diabetes mellitus. HF: heart failure. CABG: coronary artery bypass grafting. MAZE: heart surgery for atrial fibrillation. QALY: quality adjusted life year. [1]We assumed all patients in the starting population did not have previous valve replacement or CVA because it was not available or there were many missing values in the database. [2]Not available in the database, but considering the high age of these patients we assume they all received a bioprosthesis.

Table S2. Definitions of parameters

BASELINE CHARACTERISTICS	
Patient related	
Age*	Continuous
Sex	Male = 1; female = 0
Previous cardiac surgery*	Previous cardiac surgery in which the pericardium was opened.
Previous valve replacement*	Previous surgery where the heart valve was replaced.
Preoperative serum creatinine level > 200 µmol/l	The last recorded preoperative serum creatinine level of the blood was higher than 200 µmol/l.
Left ventricular (LV) function	The percentage of the end-systolic volume of the blood in the left ventricle with respect to the final diastolic volume. Higher left ventricle ejection fraction (LVEF), reflects better LV function.
Chronic obstructive pulmonary disease (COPD)	Chronic obstructive pulmonary disease
Peripheral vascular disease (PVD)	When one or more of the following criteria are fulfilled: - Claudication; - Carotid occlusion or >50% stenosis; - Amputation due to arterial disease; - Previous or planned surgery on abdominal aorta, arteries of the limbs or carotids.
Neurological dysfunction	Disease that impairs daily functioning severely.
Previous cerebrovascular accident (CVA)*	History of CVA with or without residual injury.
Preoperative endocarditis*	At the moment of the heart valve replacement the patient is being treated with antibiotics for endocarditis.
Instable angina pectoris	Angina pectoris that requires intravenous nitrate therapy until entering the operation theatre.
Pulmonary hypertension	Condition of increased blood pressure within the arteries of the lungs.
Co-morbidity categories in cost-analyses	Comorbidities were based on Pharmacy Cost Groups, which is an outpatient morbidity measure based on prior use of prescribed drugs as marker for chronic conditions.
- COPD, diabetes mellitus (DM), kidney disease and/or heart failure (HF)	Patients with COPD, DM, kidney disease and/or HF.
- Hypertension	Patients without COPD, DM, kidney disease and/or HF, but with hypertension.
- Other comorbidities	Patients with other comorbidities than COPD, DM, kidney disease, HF or hypertension.
- No comorbidities	Patients without comorbidities.
Socioeconomic status	Based on status scores reflecting the SES of a district (defined by postal code) based on characteristics of its residents: education, income, and position on the labor market. The status scores were divided in four groups based on percentiles, with lower percentiles representing lower SES.
Procedure related	
Emergency procedure	Unplanned intervention that cannot wait until the beginning of the next working day due to medical reasons.
Concomitant procedures	Procedures that are performed at the same time of the valve replacement.
- Coronary artery bypass grafting (CABG)	Coronary artery bypass grafting.
- Other valve replacement	Replacement of more than one valve.
- Other valve repair	Repair of another valve than the valve being replaced.
- Aortic root procedure	Intervention on the aortic root (part of the aorta from the aortic valve until the sinotubular junction) only.
- Aorta ascendens procedure	Intervention on the aorta ascendens (part of the aorta from the aortic valve until the arteria anonyma) only.

Table S2. Continued

BASELINE CHARACTERISTICS	
- Bentall procedure	Intervention involving composite graft replacement of the aortic valve, aortic root and ascending aorta, with re-implantation of the coronary arteries into the graft.
- Aortic arch procedure	Intervention on the aortic arch (part of the aorta beyond the arteria anonyma until the arteria subclavia sinistra).
- Aorta descendens procedure	Intervention on the aorta (part of the aorta beyond the subclavian sinister artery until beyond the diaphragm.
- Thoracic aorta surgery	Surgical intervention on the aorta ascendens, arch or descendens.
- Maze procedure	Surgical treatment for atrial fibrillation.
EVENTS	
Stroke	Stroke with or without residual injury.
Myocardial infarction (MI)†	Perioperative myocardial infarction (MI). MIs were registered according to the definition used in the STS Adult Cardiac Surgery Database.[5]
Vascular complication†	All arterial vascular complications, such as dissection of the aorta, acute ischemia of the arm or leg due to vascular problems, IABP complications, etc.
Bleeding	Any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g., vision loss) or necessitates transfusion.[6]
Atrial fibrillation (AF)/arrhythmias†	In the Adult Cardiac Surgery database, atrial fibrillations were not separately recorded. Therefore we used the registrations of arrhythmias including all forms of arrhythmia requiring treatment (such as resuscitation because of cardiac arrest or new onset atrium fibrillation or flutter that necessitates intervention (defibrillation or medication)). Spontaneous transient periods of atrial fibrillation without any consequence for the patient were not registered. Costs and utilities were based on atrial fibrillations, instead of all arrhythmias.
Pacemaker implantation (PI)†	Implantation of a medical device that uses electrical impulses, delivered by electrodes contracting the heart muscles, to regulate the beating of the heart.
Acute kidney injury (AKI)†	Renal failure was registered in the Adult Cardiac Surgery Database if one or more of the following criteria were fulfilled during the postoperative period: renal replacement treatment (dialysis, CVVH) not existing before procedure and/or highest postoperative serum creatinine level > 177 µmol/L and doubled preoperative level. This narrow definition does not include acute kidney injury stage 1 as defined by the AKIN classification in VARC-2.[7]
Structural valve deterioration (SVD)	Dysfunction or deterioration involving the operated valve (exclusive of infection or thrombosis), referring to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components of a prosthetic valve.[6]
Non-structural valve dysfunction (NSVD)	Any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the operated valve or hemolysis.[6]
Prosthetic valve thrombosis	Any thrombus not caused by infection attached to or near an operated valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment.[6]
Prosthetic valve endocarditis	Any infection involving a prosthetic valve.[6]
Re-intervention	Any surgical or transcatheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted prosthesis.[6]

*Not stable over time. †Events are only included during the first 30 days after the intervention.

Table S3. Specification of type of equation per outcome

Equation number	Outcome	Type of equation
Early mortality after SAVR		
1	Probability of early mortality	Generalized linear model with binominal family (glm function in R) Probability early mortality = age + male gender + previous cardiac surgery + preoperative serum creatinine level > 200 µmol/l + LVEF 30-50% + LVEF <30% + COPD + PVD + neurological dysfunction + emergency procedure + concomitant CABG + concomitant aorta root procedure + concomitant Bentall procedure + concomitant aorta ascendens procedure.
Early events after SAVR (separate models with same predictor variables for patients that survive or do not survive the first 30 days after the intervention)		
2	Probability of early CVA	Generalized linear model with binominal family (glm function in R) Probability early CVA = age + male gender + previous CVA + previous cardiac surgery + preoperative serum creatinine level > 200 µmol/l + LVEF 30-50% + LVEF <30% + COPD + PVD + neurological dysfunction + instable angina pectoris + pulmonary hypertension + preoperative endocarditis + emergency procedure + concomitant other valve replacement + concomitant CABG + concomitant aorta ascendens procedure.
3	Probability of early renal failure	Generalized linear model with binominal family (glm function in R) Probability early renal failure = age + male gender + previous CVA + previous cardiac surgery + preoperative serum creatinine level > 200 µmol/l + LVEF 30-50% + LVEF <30% + COPD + PVD + emergency procedure + concomitant CABG.
4	Probability of early arrhythmias	Generalized linear model with binominal family (glm function in R) Probability early arrhythmias = age + male gender + previous cardiac surgery + preoperative serum creatinine level > 200 µmol/l + LVEF 30-50% + LVEF <30% + COPD + PVD + emergency procedure + concomitant other valve replacement + concomitant CABG + concomitant aorta ascendens procedure + concomitant aorta descendens procedure + concomitant aorta arch procedure.
5	Probability of early MI	Generalized linear model with binominal family (glm function in R) Probability early MI = age + male gender + previous cardiac surgery + preoperative serum creatinine level > 200 µmol/l + LVEF 30-50% + LVEF <30% + PVD + emergency procedure + concomitant other valve replacement + concomitant CABG.
Healthcare costs		
6	Intervention costs	Generalized linear model with gamma distribution and identity link (PROC GENMOD in SAS) Intervention costs = valve position + concomitant procedures + age group + male gender + co-morbidity category + SES class + death within 6 months after the intervention.
7	Event costs (AKI, AF, stroke, MI, PI, re-intervention)	Generalized linear model with gamma distribution and identity link (PROC GENMOD in SAS) Event costs = age group + male gender + co-morbidity category + SES class + death within 6 months after the complication.
8	Other healthcare costs	Multilevel generalized linear model for with normal distribution and identity link (PROC GLIMMIX in SAS) Other healthcare costs adults = time since intervention + death + age group at intervention + male gender + SES class + AF + AKI + stroke + TIA + endocarditis + MI + PI + re-intervention. Other healthcare costs children = time since intervention + male gender + SES class.

Table S4. Continued

Equation number	Outcome	Type of equation
Societal costs		
9	Productivity costs of unpaid work	Generalized linear models with binominal family (glm function in R) Probability of unpaid work after SAVR = age + male + years since intervention + biological valve (compared to mechanical valve) + concomitant CABG + multiple valve replacement. Probability of unpaid work after TAVI = age + male + years since intervention Probability of less unpaid work after SAVR = age + male + years since intervention + biological valve (compared to mechanical valve) + concomitant CABG + multiple valve replacement. Probability of less unpaid work after TAVI = age + male + years since intervention + biological valve (compared to mechanical valve) + concomitant CABG + multiple valve replacement. Productivity costs unpaid work last four weeks after SAVR = age + male + years since intervention + biological valve (compared to mechanical valve) + concomitant CABG + multiple valve replacement. Generalized linear model with gamma family and log link (glm function in R) Estimated productivity costs last four weeks = probability of unpaid work * probability of less unpaid work * estimated productivity costs of less unpaid work
10	Informal care costs	Probability of using informal care after SAVR = age + male + years since intervention + biological valve (compared to mechanical valve) + concomitant CABG + multiple valve replacement. Probability of using informal care after TAVI = age + male + years since intervention Generalized linear model with gamma family and inverse link (glm function in R) Informal care costs per week after SAVR = age + male + years since intervention + biological valve (compared to mechanical valve) + concomitant CABG + multiple valve replacement. Informal care costs per week after TAVI = age + male + years since intervention Estimated informal care cost per week = probability of using informal care * informal care costs per week
Utilities		
12	Probability of having utility 1	Generalized linear model with binominal family (glm function in R) Probability utility of 1 after SAVR = age + male sex + years since SAVR + biological valve prosthesis + concomitant CABG + concomitant other valve replacement + previous valve replacement Probability utility of 1 after TAVI = age + male sex + years since TAVI + transfemoral approach
13	Utility below 1	Generalized linear model with gamma family and log link (glm function in R) Utility below 1 after SAVR = age + male sex + years since SAVR + biological valve prosthesis + concomitant CABG + concomitant other valve replacement + previous valve replacement Utility below 1 after TAVI = age + male sex + years since TAVI + transfemoral approach

Table S4. Logistic regression model of early mortality after aortic valve replacement (AVR) in the Adult Cardiac Surgery Database

	Early mortality (n=35,732)			
	Estimate (log odds)	**Odds ratio (OR)**	**CI 2.5% OR**	**CI 97.5% OR**
Intercept	-6.712	0.001	0.001	0.002
Preoperative risk factors				
Age	0.037	1.038	1.031	1.045
Gender, male	-0.450	0.637	0.564	0.720
Previous cardiac surgery	1.069	2.912	2.486	3.411
Preoperative serum creatinine level > 200 µmol/l	0.926	2.525	1.950	3.270
LV function (compared to LVEF >50%)				
LVEF 30-50%	0.450	1.569	1.368	1.799
LVEF <30%	0.848	2.335	1.879	2.900
COPD	0.557	1.746	1.513	2.016
Peripheral vascular disease	0.478	1.613	1.390	1.872
Neurological dysfunction	0.409	1.505	1.155	1.961
Procedure related risk factors				
Emergency procedure	1.919	6.814	5.694	8.154
Concomitant CABG	0.677	1.967	1.737	2.229
Concomitant aorta root procedure	0.514	1.672	1.036	2.699
Concomitant Bentall procedure	0.917	2.503	1.969	3.181
Concomitant aorta ascendens procedure	0.705	2.024	1.304	3.141

CI: confidence interval. OR: odds ratio. LV: left ventricle. LVEF: left ventricular ejection fraction. COPD: chronic obstructive pulmonary disease. CABG: coronary artery bypass grafting.

Table S5. Logistic regression of risk on stroke during the first 30 days in patients that survive or do not survive the first 30 days after the intervention

	Stroke in patients that do not survive first 30 days (complete cases n=417)					Stroke in patients that survive first 30 days (complete cases n=13087)				
	Estimate (log odds)	Odds ratio (OR)	CI 2.5% (OR)	CI 97.5% (OR)	p-value	Estimate (log odds)	Odds ratio (OR)	CI 2.5% (OR)	CI 97.5% (OR)	p-value
Intercept	0.471	1.601	3.418	1.466	0.702	-5.301	0.005	0.002	0.014	0.000
Age	-0.041	0.960	1.016	0.079	0.011	0.021	1.021	1.035	1.021	0.002
Male	0.282	1.326	1.378	2.410	0.379	-0.489	0.614	0.614	0.614	0.000
Previous CVA	0.133	1.142	1.622	1.316	0.784	0.510	1.665	1.665	1.665	0.004
Previous cardiac surgery	-0.267	0.765	1.545	0.541	0.539	0.682	1.979	1.979	1.979	0.000
Preoperative serum creatinine level > 200 µmol/l	-1.289	0.276	2.983	0.307	0.238	-0.190	0.827	0.827	0.827	0.717
LV function: LVEF > 50%	1.207	3.345	1.506	19.107	0.003	-0.183	0.833	0.833	0.833	0.215
COPD	-0.566	0.568	1.557	0.278	0.201	0.112	1.119	1.119	1.119	0.524
PVD	-0.156	0.855	1.533	0.694	0.714	0.212	1.236	1.236	1.236	0.244
Neurological dysfunction	-0.485	0.616	2.019	0.502	0.490	0.506	1.658	1.658	1.658	0.088
Instable angina pectoris	1.660	5.257	2.176	8.456	0.033	0.136	1.146	1.146	1.146	0.684
Pulmonary hypertension	-0.917	0.400	3.104	0.445	0.418	-0.139	0.870	0.870	0.870	0.820
Endocarditis	-0.239	0.787	1.628	0.612	0.624	-0.638	0.529	0.529	0.529	0.216
Emergency surgery	-0.022	0.978	1.484	0.945	0.955	-0.627	0.534	0.534	0.534	0.084
Concomitant other valve replacement	-0.847	0.429	1.800	0.237	0.150	1.338	3.811	3.811	3.811	0.000
Concomitant CABG	-0.489	0.613	1.395	0.230	0.142	0.409	1.505	1.505	1.505	0.002
Concomitant aorta ascendens procedure	0.480	1.617	1.783	2.295	0.406	0.425	1.529	1.529	1.529	0.179
Apparent AUC	**0.724**					**0.662**				
Optimism	**0.073**					**0.027**				
Bootstrapped AUC	**0.651**					**0.636**				

CI: confidence interval. OR: odds ratio. CVA: cerebrovascular accident. LV: left ventricle. LVEF: left ventricular ejection fraction. COPD: chronic obstructive pulmonary disease. PVD: peripheral vascular disease. CABG: coronary artery bypass grafting. AUC: area under the curve.

Table S6. Logistic regression of early risk on renal failure during the first 30 days in patients that survive or do not survive the first 30 days after the intervention

	Renal failure in patients that do not survive first 30 days (complete cases n=622)					Renal failure in patients that survive first 30 days (complete cases n=17191)				
	Estimate (log odds)	**Odds ratio (OR)**	**CI 2.5% (OR)**	**CI 97.5% (OR)**	**p-value**	**Estimate (log odds)**	**Odds ratio (OR)**	**CI 2.5% (OR)**	**CI 97.5% (OR)**	**p-value**
Intercept	-2.507	0.081	0.014	0.485	0.006	-5.683	0.003	0.002	0.007	0.000
Age	0.011	1.011	0.987	1.035	0.375	0.018	1.018	1.008	1.028	0.000
Male	-0.092	0.912	0.593	1.402	0.674	0.229	1.258	1.006	1.573	0.045
Previous cardiac surgery	-0.183	0.833	0.482	1.441	0.514	1.059	2.884	2.254	3.690	0.000
Preoperative serum creatinine level > 200 µmol/l	0.459	1.583	0.678	3.694	0.288	1.968	7.154	5.109	10.019	0.000
LV function (compared to LVEF >50%)										
LVEF 30-50%	0.175	1.191	0.736	1.926	0.477	0.312	1.367	1.079	1.731	0.010
LVEF <30%	-0.519	0.595	0.254	1.396	0.233	0.785	2.193	1.490	3.228	0.000
COPD	0.197	1.218	0.730	2.031	0.451	0.377	1.458	1.127	1.888	0.004
PVD	0.124	1.132	0.674	1.902	0.639	0.530	1.699	1.312	2.200	0.000
Emergency surgery	0.444	1.559	0.904	2.689	0.110	1.477	4.380	3.144	6.100	0.000
Concomitant CABG	0.154	1.166	0.747	1.822	0.499	0.001	1.001	0.802	1.250	0.990
Apparent AUC	**0.583**					**0.723**				
Optimism	**0.070**					**0.012**				
Bootstrapped AUC	**0.513**					**0.711**				

CI: confidence interval. OR: odds ratio. LV: left ventricle. LVEF: left ventricular ejection fraction. COPD: chronic obstructive pulmonary disease. PVD: peripheral vascular disease. CABG: coronary artery bypass grafting. AUC: area under the curve.

Table S7. Logistic regression of early risk on arrhythmias during the first 30 days in patients that survive or do not survive the first 30 days after the intervention

	Arrhythmias in patients that do not survive first 30 days (complete cases n=623)					Arrhythmias in patients that survive first 30 days (complete cases n=17192)				
	Estimate (log odds)	**Odds ratio (OR)**	**CI 2.5% (OR)**	**CI 97.5% (OR)**	**p-value**	**Estimate (log odds)**	**Odds ratio (OR)**	**CI 2.5% (OR)**	**CI 97.5% (OR)**	**p-value**
Intercept	-1.953	0.142	0.030	0.677	0.014	-2.235	0.107	0.085	0.135	0.000
Age	0.016	1.016	0.995	1.038	0.125	0.024	1.024	1.021	1.028	0.000
Male	-0.568	0.566	0.392	0.819	0.003	0.050	1.051	0.984	1.124	0.141
Previous cardiac surgery	-0.075	0.927	0.580	1.482	0.752	-0.066	0.936	0.838	1.046	0.244
Preoperative serum creatinine level > 200 µmol/l	0.917	2.501	1.194	5.242	0.015	0.013	1.013	0.793	1.294	0.919
LV function (compared to LVEF >50%)										
LVEF 30-50%	-0.027	0.973	0.632	1.498	0.903	0.062	1.064	0.980	1.156	0.140
LVEF <30%	0.213	1.237	0.656	2.332	0.511	0.144	1.154	0.976	1.366	0.094
COPD	0.217	1.243	0.798	1.936	0.337	0.062	1.064	0.970	1.166	0.190
PVD	-0.211	0.810	0.500	1.310	0.390	-0.010	0.990	0.894	1.097	0.851
Emergency surgery	-0.183	0.833	0.484	1.433	0.509	0.014	1.014	0.831	1.237	0.891
Concomitant other valve replacement	-0.067	0.935	0.545	1.606	0.808	0.548	1.729	1.466	2.039	0.000
Concomitant CABG	0.247	1.280	0.868	1.887	0.213	0.015	1.015	0.948	1.087	0.667
Concomitant aorta ascendens procedure	0.077	1.080	0.391	2.988	0.882	0.197	1.217	0.989	1.497	0.063
Concomitant aorta descendens procedure	1.888	6.603	0.826	52.787	0.075	0.107	1.113	0.466	2.654	0.810
Concomitant aortic arch procedure	-0.889	0.411	0.150	1.125	0.084	-0.205	0.814	0.657	1.010	0.061
Apparent AUC	**0.641**					**0.573**				
Optimism	**0.046**					**0.004**				
Bootstrapped AUC	**0.595**					**0.569**				

CI: confidence interval. OR: odds ratio. LV: left ventricle. LVEF: left ventricular ejection fraction. COPD: chronic obstructive pulmonary disease. PVD: peripheral vascular disease. CABG: coronary artery bypass grafting. AUC: area under the curve.

Table S8. Logistic regression of early risk on MI during the first 30 days in patients that survive or do not survive the first 30 days after the intervention

	MI in patients that do not survive first 30 days (complete cases n=505)					MI in patients that survive first 30 days (complete cases n=13,831)				
	Estimate (log odds)	Odds ratio (OR)	CI 2.5% (OR)	CI 97.5% (OR)	p-value	Estimate (log odds)	Odds ratio (OR)	CI 2.5% (OR)	CI 97.5% (OR)	p-value
Intercept	0.354	1.425	0.152	13.343	0.756	-4.315	0.013	0.005	0.039	0.000
Age	-0.036	0.965	0.935	0.995	0.023	-0.010	0.990	0.975	1.005	0.185
Male	-0.584	0.558	0.308	1.010	0.054	-0.223	0.800	0.577	1.109	0.181
Previous cardiac surgery	-0.753	0.471	0.158	1.402	0.176	0.631	1.880	1.117	3.164	0.018
LV function (compared to LVEF >50%)						-0.160	0.852	0.563	1.291	0.451
LVEF 30-50%	-0.075	0.927	0.465	1.848	0.830	-0.330	0.719	0.291	1.777	0.475
LVEF <30%	-0.678	0.508	0.143	1.801	0.294	0.328	1.388	0.920	2.096	0.118
PVD	-0.259	0.772	0.355	1.680	0.514	1.086	2.962	1.515	5.792	0.002
Emergency surgery	-0.486	0.615	0.248	1.527	0.295	-0.601	0.548	0.158	1.903	0.344
Concomitant other valve replacement	-0.107	0.899	0.152	5.324	0.906	1.301	3.674	2.602	5.188	0.000
Concomitant CABG	1.100	3.003	1.535	5.875	0.001	-4.315	0.013	0.005	0.039	0.000
Apparent AUC	**0.684**					**0.677**				
Optimism	**0.061**					**0.008**				
Bootstrapped AUC	**0.622**					**0.669**				

CI: confidence interval. OR: odds ratio. LV: left ventricle. LVEF: left ventricular ejection fraction. PVD: peripheral vascular disease. CABG: coronary artery bypass grafting. AUC: area under the curve.

Table S9. Multilevel generalized linear model for the other annual healthcare costs after SVR in postintervention years 1 through 4

Other healthcare costs	**Adults (n=17,553)**		
Parameter	**β**	**95% CI**	**P-value**
Intercept	11,662	10,315-13,009	<.0001
Time (compared to year 1 excluding intervention costs)			
Year 2	-3,461	-4,308--2,614	<.0001
Year 3	-2,372	-3,920--0,823	0.003
Year 4	-0,243	-2,252-1,766	0.812
Death	3,845	2,672-5,018	<.0001
Age at intervention (compared to elderly)			
Young adults	-1,070	-2,123--0,017	0.046
Middle aged	-2,373	-3,242--1,505	<.0001
Male	-0,940	-1,694--0,185	0.015
Co-morbidity (compared to no co-morbidity)			
COPD, DM, kidney disease and/or HF	6,357	5,216-7,498	<.0001
Hypertension	1,378	0,207-2,548	0.021
Other comorbidities	1,964	0,289-3,639	0.022
SES[1] (compared to highest SES: 71-100)			
0-20	1,235	0,174-2,295	0.023
21-40	0,320	-0,741-1,381	0.554
41-70	0,833	-0,125-1,791	0.088
Complications			
AF	747	-0,485-1,979	0.235
AKI	8,178	5,371-10,985	<.0001
Stroke	4,506	3,038-5,974	<.0001
MI	5,677	2,005-9,350	0.002
PI	3,430	1,438-5,423	0.001

CI: confidence interval. SVR: surgical valve replacement. COPD: Chronic Obstructive Pulmonary Disease. DM: diabetes mellitus. HF: heart failure. SES: socioeconomic status. AF: atrial fibrillation. AKI: acute kidney injury. TIA: transient ischemic attack. MI: myocardial infarction. PI: pacemaker implantation.
[1]Higher percentiles represent higher SES.

Table S10. Regression analyses of productivity costs of unpaid work in SAVR patients

A. Probability unpaid work	SAVR (n=625)			TAVI (n=213)		
	Coefficient	Odds ratio (95% CI)	p-value	Coefficient	Odds ratio (95% CI)	p-value
Intercept	-0.742	0.476 (0.165-1.375)	0.170	0.117	1.124 (0.030-42.508)	0.950
Age	0.003	1.003 (0.986-1.021)	0.720	-0.016	0.984 (0.941-1.028)	0.470
Male	0.117	1.125 (0.776-1.629)	0.535	0.672	1.959 (1.026-3.739)	0.041
Years since intervention	0.061	1.063 (0.969-1.166)	0.196	-0.035	0.966 (0.804-1.161)	0.712
Biological valve (compared to mechanical)	-0.057	0.945 (0.593-1.505)	0.812			
Concomitant CABG	0.269	1.308 (0.881-1.943)	0.182			
Multiple valve replacement	0.188	1.207 (0.692-2.105)	0.508			
B. Probability less unpaid work	**SAVR (n=257)**			**TAVI (n=65)[1]**		
	Coefficient	Odds ratio (95% CI)	p-value	Coefficient	Odds ratio (95% CI)	p-value
Intercept	2.609	13.582 (1.745-105.694)	0.013	-2.657	0.070 (0.030-0.164)	0.000
Age	-0.050	0.952 (0.919-0.985)	0.005			
Male	-0.182	0.834 (0.419-1.661)	0.605	-0.260	0.771 (0.305-1.947)	0.582
Years since intervention	-0.253	0.776 (0.648-0.930)	0.006	0.183	1.200 (0.961-1.500)	0.108
Biological valve (compared to mechanical)	0.700	2.014 (0.832-4.872)	0.121			
Concomitant CABG	-0.504	0.604 (0.278-1.316)	0.205			
Multiple valve replacement	-0.360	0.698 (0.219-2.221)	0.542			
C. Estimated productivity costs unpaid work last four weeks	**SAVR (n=57)**			**TAVI (n=16)[2]**		
	Coefficient	Exponentiated coefficient† (95% CI)	p-value	Mean productivity costs of unpaid work in all patients with less unpaid work		
Intercept	6.272	529.373 (136.433-2054.015)	0.000	€648±€797		
Age	-0.003	0.997 (0.974-1.021)	0.807			
Male	0.068	1.070 (0.614-1.864)	0.812			
Years since intervention	-0.104	0.901 (0.781-1.040)	0.161			
Biological valve (compared to mechanical)	0.763	2.145 (1.084-4.242)	0.033			
Concomitant CABG	-0.535	0.586 (0.295-1.163)	0.133			
Multiple valve replacement	1.223	3.398 (1.284-8.995)	0.017			

SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve implantation. CI: confidence interval. CABG: coronary artery bypass grafting. †The exponentiated coefficient is the factor by which the arithmetic mean outcome on the original scale is multiplied. N.B. The results should be interpreted as follows, for example for sex: males are more likely to have unpaid work than females (logistic regression model 1), are less likely to be unable to perform unpaid work (logistic regression model 2) and when all other variables are equal, the mean estimated productivity costs of males is almost equal to females(GLM). [1]Age excluded because number of events (n=21) was too small for three predictors. [2]The productivity costs of patients who performed less unpaid work after TAVI was only reported for 16 of the 21 patients with less unpaid work. Therefore we apply the average productivity costs of unpaid work in these patients to all patients instead of using a GLM.

Table S11. Regression analyses of informal care use and costs

	SAVR (n=625)			TAVI (n=248)		
A. Probability of using informal care	**Coefficient**	**Odds ratio (95% CI)**	**p-value**	**Coefficient**	**Odds ratio (95% CI)**	**p-value**
Intercept	-1.179	0.308 (0.071-1.334)	0.115	0.402	1.495 (0.062-36.225)	0.805
Age	0.012	1.012 (0.987-1.038)	0.334	-0.004	0.996 (0.958-1.035)	0.847
Male	-0.678	0.508 (0.323-0.797)	0.003	-0.767	0.464 (0.270-0.798)	0.005
Years since intervention	-0.318	0.727 (0.639-0.828)	0.000	-0.141	0.868 (0.735-1.027)	0.099
Biological valve (compared to mechanical)	-0.111	0.895 (0.476-1.684)	0.731			
Concomitant CABG	-0.134	0.874 (0.515-1.484)	0.619			
Multiple valve replacement	0.442	1.556 (0.798-3.032)	0.194			
	SAVR (n=97)			**TAVI (n=86)**		
B. Estimated informal care costs/week (gamma family, inverse link)	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
Intercept	0.002	-0.002-0.007	0.326	0.003	-0.004-0.010	0.383
Age	0.000	0.000-0.000	0.336	0.000	0.000-0.000	0.488
Male	-0.001	-0.002-0.001	0.508	-0.003	-0.004--0.001	0.002
Years since intervention	0.000	0.000-0.000	0.897	0.000	0.000-0.000	0.902
Biological valve (compared to mechanical)	-0.002	-0.004-0.000	0.098			
Concomitant CABG	0.001	-0.001-0.003	0.562			
Multiple valve replacement	-0.001	-0.003-0.001	0.177			

SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve implantation. CI: confidence interval. CABG: coronary artery bypass grafting. The results should be interpreted as follows, for example in the models for SAVR patients: males are less likely to use informal care than females (logistic regression model) and when all other variables are equal, the mean estimated informal care costs of males is 0.001 times (i.e. 0.1%) lower than for females (GLM).

Table S12. Length of hospital stay after events

Event	Length of hospital stay (LOS)
Bleeding	2 days [8]
Prosthetic valve dysfunction without re-intervention	8.67 days [9]
Valve thrombosis	10 days
Endocarditis	6 weeks

Table S13. Median structural valve deterioration (SVD) free life expectancy in various scenarios

	SAVR	TAVI
Current valve prostheses	9.4	4.6
- Subgroup patients aged 70-80 years	10.4	6.9
- Subgroup patients aged >80 years	6.4	3.7
Improved durability of TEHV		
No prosthetic valve dysfunction events	lifetime	lifetime
75% less prosthetic valve dysfunction events	9.9	4.7
50% less prosthetic valve dysfunction events	9.9	4.7
25% less prosthetic valve dysfunction events	9.6	4.7
Perfect TEHV (no prosthetic valve related events)	lifetime	lifetime
Improved TEHV (50% less prosthetic valve related events)	10.0	4.7
- Subgroup patients aged 70-80 years	11.0	7.7
- Subgroup patients aged >80 years	6.6	3.8
Decreased durability (50% more events) but improvements in thrombogenicity and infection resistance (50% less events)	9.0	4.5

SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve implantation. TEHV: tissue-engineered heart valves.

Table S14. Cumulative cost savings per year in the first 10 years after introduction of TEHV with varying substitution rates

	SAVR (n=1,931/year)				TAVI (n=809/year)				TAVI (n=3,745/year)			
Substitution rate TEHV	25%	50%	75%	100%	25%	50%	75%	100%	25%	50%	75%	100%
Years												
1	57,124	114,247	171,371	228,495	7,606	15,212	22,818	30,424	35,210	70,419	105,629	140,839
2	192,446	384,891	577,337	769,782	25,012	50,024	75,035	100,047	115,784	231,568	347,352	463,136
3	389,685	779,369	1,169,054	1,558,738	51,834	103,667	155,501	207,335	239,947	479,894	719,840	959,787
4	628,621	1,257,242	1,885,863	2,514,484	91,706	183,413	275,119	366,825	424,524	849,049	1,273,573	1,698,098
5	910,997	1,821,995	2,732,992	3,643,989	148,536	297,071	445,607	594,143	687,597	1,375,195	2,062,792	2,750,389
6	1,224,539	2,449,078	3,673,616	4,898,155	226,671	453,343	680,014	906,686	1,049,301	2,098,602	3,147,902	4,197,203
7	1,569,697	3,139,393	4,709,090	6,278,786	326,901	653,802	980,703	1,307,604	1,513,281	3,026,561	4,539,842	6,053,123
8	1,953,514	3,907,028	5,860,543	7,814,057	439,586	879,171	1,318,757	1,758,343	2,034,918	4,069,835	6,104,753	8,139,671
9	2,364,815	4,729,630	7,094,444	9,459,259	561,726	1,123,452	1,685,177	2,246,903	2,600,325	5,200,650	7,800,975	10,401,300
10	2,809,036	5,618,071	8,427,107	11,236,142	692,159	1,384,317	2,076,476	2,768,635	3,204,121	6,408,243	9,612,364	12,816,485

Costs in Euros. SAVR: surgical aortic valve replacement. TAVI: transcatheter aortic valve implantation. TEHV: tissue-engineered heart valves.

Table S15. Mean age and proportion of patients with concomitant CABG in age and sex subgroups in the simulation model and observed data from the Providence Health System.

	Mean age (years)		Concomitant CABG (%)	
Subgroups by age and sex	**Simulation**	**Observed**	**Simulation**	**Observed**
70-80 years - males	74.9	75.1	49	56
70-80 years - females	75.3	75.4	35	39
>80 years - males	82.2	84.2	53	63
>80 years - females	82.4	84.3	39	48

CABG: coronary artery bypass grafting.

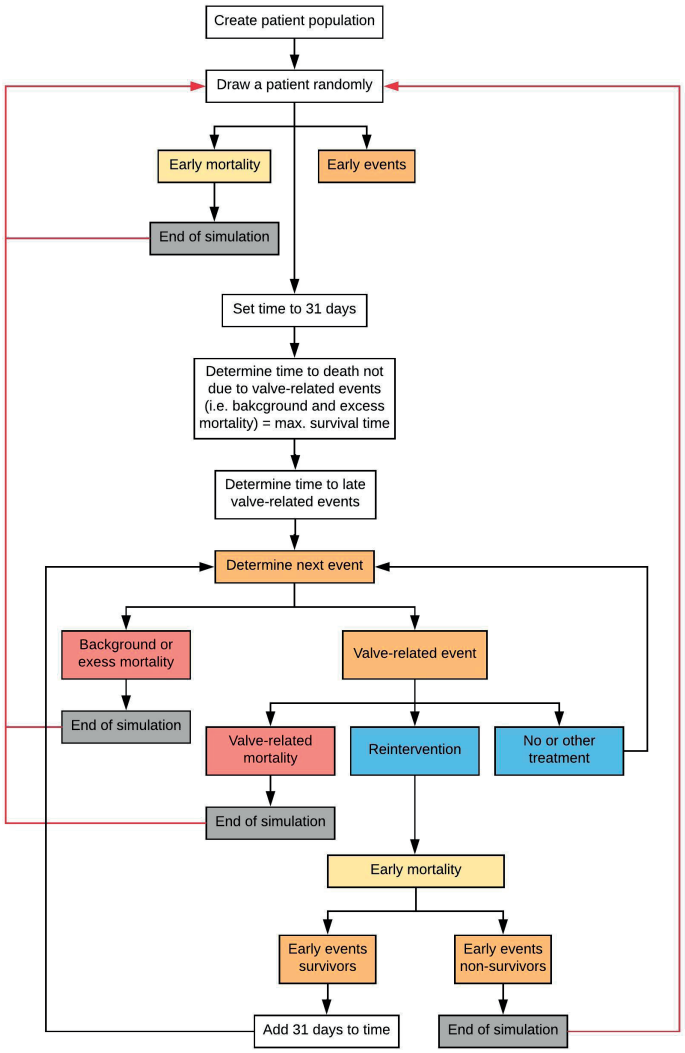


Figure S1. Flowchart patient level simulation model

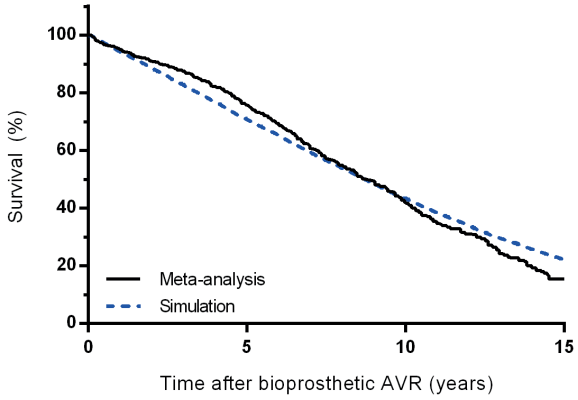


Figure S2. Internal validation of survival after SAVR with bioprostheses.

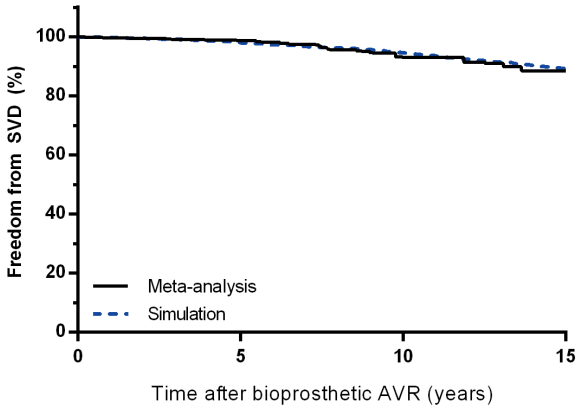


Figure S3. Internal validation of freedom from structural valve deterioration (SVD) after SAVR with bioprostheses.

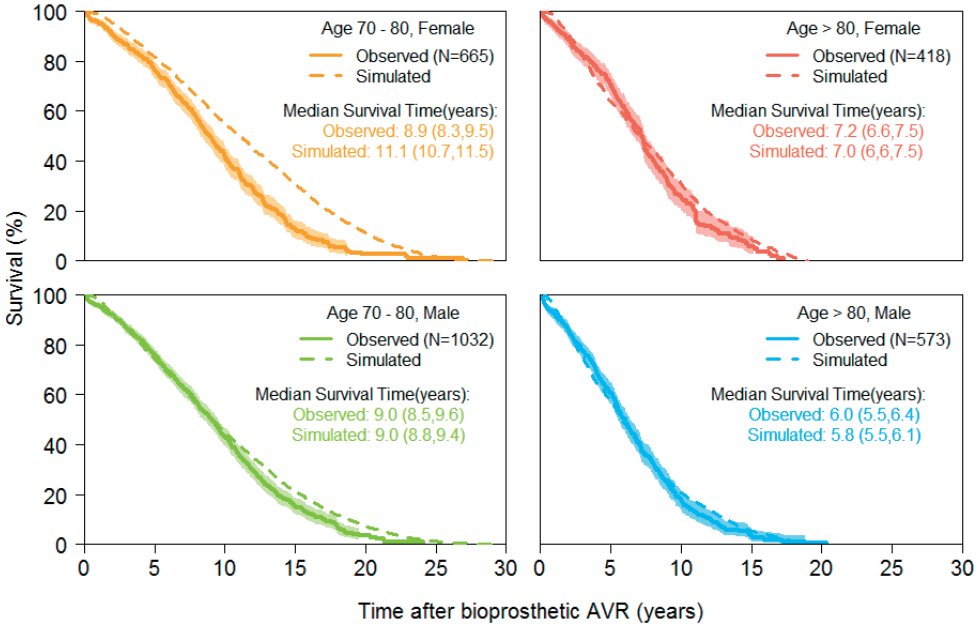


Figure S4. External validation of survival outcomes.

Comparison of patient level simulation model survival outcomes after SAVR with bioprostheses and observed survival in in the Providence Health System, Portland, US by age and sex.

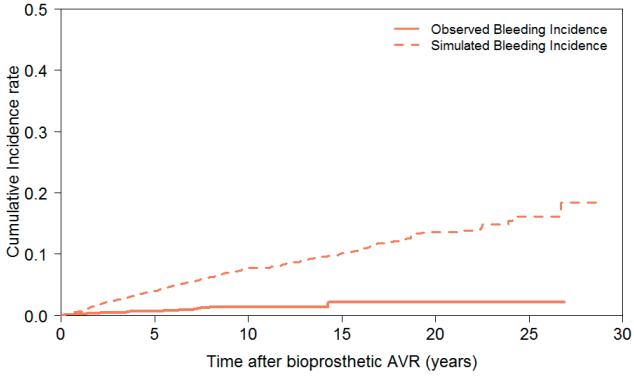


Figure S5. External validation of cumulative incidence of bleeding.

Comparison of patient level simulation model cumulative incidence of bleeding after SAVR with bioprostheses and observed cumulative incidence of bleeding in in the Providence Health System, Portland, US by age and sex.

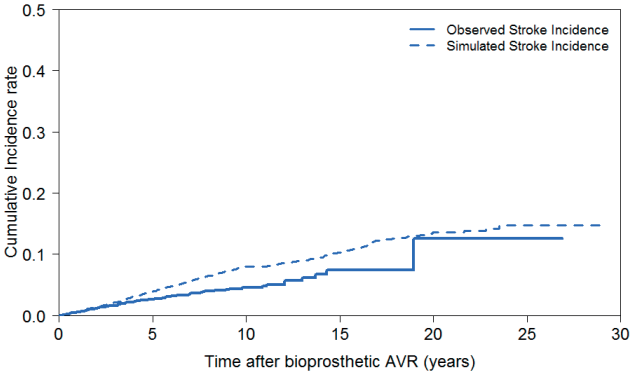


Figure S6. External validation of cumulative incidence of stroke.

Comparison of patient level simulation model cumulative incidence of stroke after SAVR with bioprostheses and observed cumulative incidence of stroke in in the Providence Health System, Portland, US by age and sex.

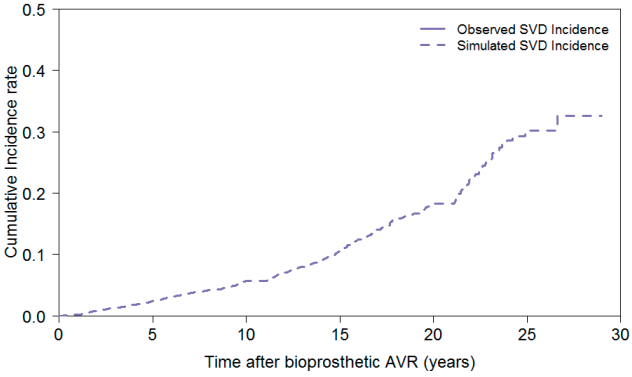


Figure S7. External validation of cumulative incidence of structural valve deterioration (SVD).

Comparison of patient level simulation model cumulative incidence of SVD after SAVR with bioprostheses and observed cumulative incidence of SVD in in the Providence Health System, Portland, US by age and sex.

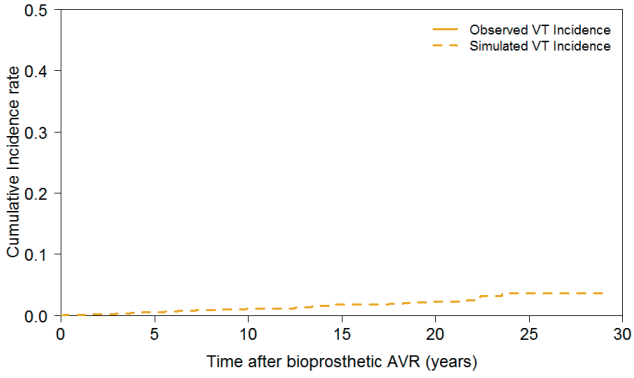


Figure S8. External validation of cumulative incidence of prosthetic valve thrombosis (VT).

Comparison of patient level simulation model cumulative incidence of VT after SAVR with bioprostheses and observed cumulative incidence of VT in in the Providence Health System, Portland, US by age and sex.

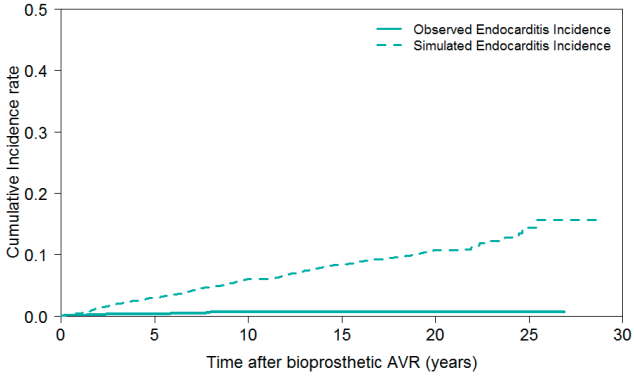
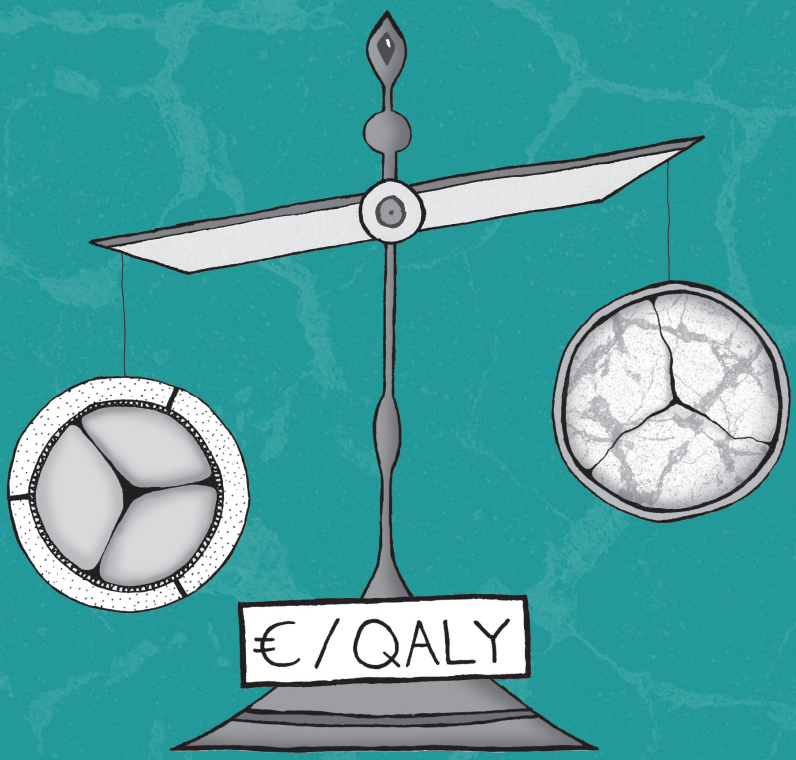


Figure S9. External validation of cumulative incidence of prosthetic valve endocarditis.

Comparison of patient level simulation model cumulative incidence of endocarditis after SAVR with bioprostheses and observed cumulative incidence of endocarditis in in the Providence Health System, Portland, US by age and sex.

References supplemental material

1. Hein, R., et al., *Outcome of patients after emergency conversion from transcatheter aortic valve implantation to surgery.* EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology, 2013. 9(4): p. 446-451.
2. Arsalan, M., et al., *Predictors and outcome of conversion to cardiac surgery during transcatheter aortic valve implantation.* European Journal of Cardio-Thoracic Surgery, 2018.
3. Ludman, P.F., et al., *Transcatheter aortic valve implantation in the UK: temporal trends, predictors of outcome and 6 year follow up: a report from the UK TAVI Registry 2007 to 2012.* Circulation, 2015: p. CIRCULATIONAHA. 114.013947.
4. O'Hagan, A., M. Stevenson, and J. Madan, *Monte Carlo probabilistic sensitivity analysis for patient level simulation models: efficient estimation of mean and variance using ANOVA.* Health economics, 2007. **16**(10): p. 1009-1023.
5. The Society of Thoracic Surgeons (STS) *STS Adult Cardiac Surgery Database Training Manual*. 2017.
6. Akins, C.W., et al., *Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions.* European Journal of Cardio-Thoracic Surgery, 2008. **33**(4): p. 523-528.
7. Kappetein, A.P., et al., *Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation: The Valve Academic Research Consortium-2 Consensus Document†.* Journal of the American College of Cardiology, 2012. **60**(15): p. 1438-1454.
8. Geisler, B.P., et al., *Cost-effectiveness and Projected Survival of Self-expanding Transcatheter versus Surgical Aortic Valve Replacement for High Risk Patients in a European Setting. A Dutch Analysis Based on the CoreValve High-Risk Trial.* Structural Heart, 2017(just-accepted).
9. Stevanović, J. and M.J. Postma, *Incidence description and costs of acute heart failure in the Netherlands.* Pharmacoeconomics of cardiovascular disease prevention, 2015: p. 73.


€/QALY

9

What is the potential of tissue-engineered pulmonary valves in children?

An early health technology assessment

Simone A. Huygens, Maureen P.M.H. Rutten-van Mölken, Anahita Noruzi, Jonathan R.G. Etnel, Isaac Corro Ramos, Carlijn V.C. Bouten, Jolanda Kluin, Johanna J.M. Takkenberg.

Ann Thorac Surg. In press.

ABSTRACT

Background: As a living heart valve substitute with growth potential and improved durability, tissue-engineered heart valves (TEHV) may prevent re-interventions that are currently often needed in children with congenital heart disease. We performed early Health Technology Assessment to assess the potential cost-effectiveness of TEHV in children requiring right ventricular outflow tract reconstruction (RVOTR).

Methods: A systematic review and meta-analysis was conducted of studies reporting clinical outcome after RVOTR with existing heart valve substitutes in children (mean age ≤12 and/or maximum age≤21 years) published between 1/1/2000-2/5/2018. Using a patient-level simulation model, costs and effects of RVOTR with TEHV compared to existing heart valve substitutes were assessed from a healthcare perspective applying a 10-year time horizon. Improvements in performance of TEHV, divided in durability, thrombogenicity, and infection resistance, were explored to estimate quality-adjusted life years (QALY) gain, cost reduction, headroom, and budget impact associated with TEHV.

Results: Five-year freedom from re-intervention after RVOTR with existing heart valve substitutes was 46.1% in patients ≤2 years old and 81.1% in patients >2 years old. Improvements in durability had the highest impact on QALYs and costs. In the 'improved TEHV performance' scenario (durability≥5 years and -50% other valve-related events), QALY gain was 0.074 and cost reduction was €10,378 per patient, translating to maximum additional costs of €11,856 per TEHV compared to existing heart valve substitutes.

Conclusions: This study showed that there is room for improvement in clinical outcomes in children requiring RVOTR. If TEHV result in improved clinical outcomes, they are expected to be cost-effective compared to existing heart valve substitutes.

INTRODUCTION

The pulmonary valve is the most commonly affected heart valve in congenital heart disease.[1] During 2014-2017, 3,488 right ventricle outflow tract reconstructions (RVOTR) were performed in the US.[2] Most children who undergo RVOTR need multiple re-interventions later in life, because existing heart valve substitutes cannot accommodate patient growth.[3] In contrast, tissue-engineering provides a promising method to create living heart valves with growth potential that may last a lifetime.[4-7] In this approach, a valve-shaped scaffold is implanted in the patients' heart that recruits cells from the bloodstream and surrounding tissues and gradually transforms into an autologous valve while the scaffold degrades.[7] Preclinical studies on the performance of tissue-engineered heart valves (TEHV) and clinical trials of tissue-engineered vascular grafts showed promising results, but results of the first-in-man clinical trial of TEHV are not available yet.[5-8] It is difficult to define minimum performance requirements of TEHV, because reports on performance of existing pulmonary valve substitutes in children are predominantly based on small single-center studies. Furthermore, when TEHV are introduced in clinical practice, healthcare decision makers do not only need assurance that TEHV improve clinical outcomes, but also that they are cost-effective compared to existing options to ensure optimal allocation of the limited healthcare budget.[9] Generating information on cost-effectiveness in early development phases can help set research priorities that ensure that TEHV will meet needs of patients, professionals, and payers. In this early Health Technology Assessment (HTA) study, we performed a systematic review and meta-analysis of published outcomes of RVOTR with existing heart valve substitutes in children and we estimated the potential cost-effectiveness, headroom and budget impact of TEHV using a patient-level simulation model.

METHODS

Systematic review and meta-analysis

Embase, MEDLINE, Cochrane Central, Google Scholar, and Web-Of-Science databases were systematically searched for studies reporting on outcomes after RVOTR with a heart valve substitute or valved conduit in children (mean age≤12 and/or maximum age≤21 years) published between 1-1-2000 and 2-5-2018. Relevant data was extracted from included studies and pooled using the inverse variance method in a random-effects model. Pooled Kaplan-Meier time-to-event meta-analysis was conducted by extrapolating and pooling estimates of individual patient time-to-event data from published Kaplan-Meier curves. Detailed descriptions of these methods are provided in Supplement 1.

Patient-level simulation

We used a patient-level simulation model to compare costs and effectiveness of TEHV with existing pulmonary valve substitutes. The patient-level simulation model was based on our previously published conceptual model (Figure 1).[10] The model simulation starts with creating a virtual patient population by random sampling (with replacement) 25,000 patients from a Dutch health insurance claims database comprising 338 children (mean±SD 4.5±5.8 years) who underwent RVOTR between 2010-2013 (Table S1).[11] The number of 25,000 sampled patients was required to get stable results. For each patient, mortality and events within 30 days after the intervention are determined. Subsequently, time to late events and death are calculated. The event with the lowest predicted time value is considered to occur after which the consequences for quality of life and costs are modelled. Then, time to late events and death are calculated again. The simulation stops when death has the lowest predicted time value of all events or when the patient dies directly after an event. This process is repeated for all patients (Figure S1). By combining data of all simulated patients, the average difference in quality-adjusted life years (QALY) and costs between TEHV and existing heart valve substitutes is calculated. The model was implemented in R3.3.2 using RStudio 1.0.136.

Mortality and events

The events included in the model are presented in Figure 1/Table S2. Mortality was divided into early mortality (≤30 days after intervention), mortality directly related to valve-related events, background mortality, and excess mortality. Background mortality was obtained for the year 2016 in the Dutch general population.[12] Excess mortality is ascribed to the potential excess risk of dying of patients who underwent heart valve interventions which can be explained by increased occurrence of sudden death, underreporting of valve-related events, and underlying associated cardiac pathology.[13] This excess mortality was expressed as hazard ratio relative to background mortality. Risks and rates of mortality and events after RVOTR, probabilities of re-intervention or death after events, and the hazard ratio of excess mortality were derived from our systematic review and meta-analysis (see Results section; Table S3). The pooled freedom from re-intervention curve was used to generate time to structural valve deterioration using a Weibull distribution and was corrected for re-interventions due to endocarditis and valve thrombosis. We were unable to determine distributions for other events based on our meta-analysis, therefore we assumed a constant hazard rate by using exponential distributions. Different input parameters were included for patients aged below or above two years at time of surgery based on the respective subgroups in our meta-analysis. When patients underwent a re-intervention during the simulation at an age above 2 years, the corresponding input parameters were applied for the rest of the simulation.

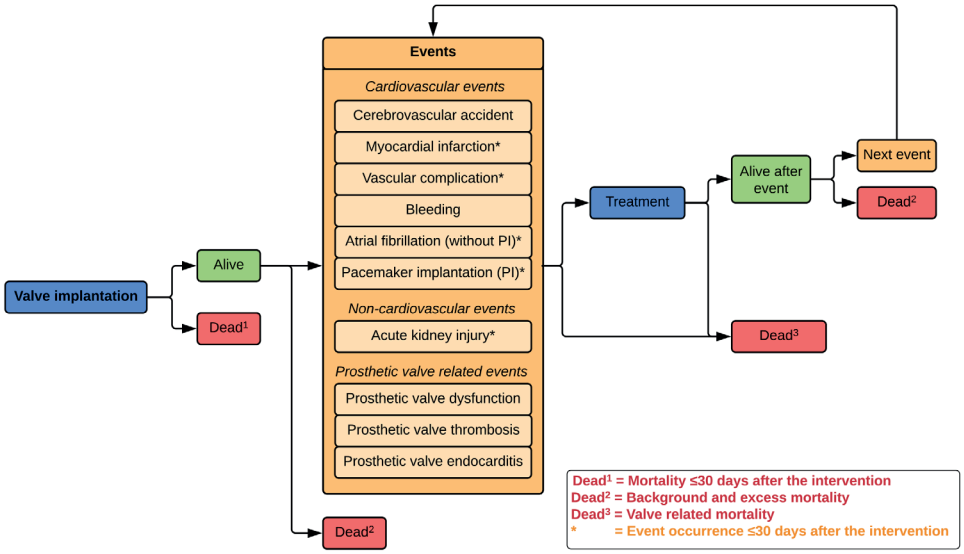


Figure 1. Conceptual model of the patient-level simulation model.

Costs

Healthcare costs included intervention, treatment of events and other healthcare use costs (Table S3). Most costs were dependent on patient and intervention characteristics using (multilevel) generalised linear models ((M)GLM)(Table S4).[11] We assumed most complications had a permanent influence on healthcare use (e.g. lifelong follow-up with cardiologist after pacemaker implantation), except for prosthetic valve related events and re-intervention to avoid double counting of follow-up costs for the initial heart valve implantation. Other healthcare costs were calculated with the MGLM regression formula within three years after the intervention (Table S5). Beyond three years, these costs were adjusted to patient age using relative increases in total healthcare costs by age and sex of the general population.[14]

Health-related quality of life

Health-related quality of life was expressed in utilities. Utility of patients after RVOTR without events was 0.852 (Supplement 2).[15] The utility was corrected for events using utility multipliers for a specific time duration after the event based on literature or assumptions (Table S3).

Tissue-engineered heart valves

Exact costs and performance of TEHV are unclear, because they are not used in clinical practice as yet. Therefore, we made the following assumptions on TEHV performance. We

assumed that safety will be established before TEHV are introduced in clinical practice, for this reason we did not include higher risks of early mortality or valve-related events. The procedure to implant TEHV is expected to be comparable to surgically implanting existing heart valve substitutes. Hence, we assumed that early mortality and event risks, which are mainly procedure-related and not valve-related, are comparable for TEHV and existing heart valve substitutes. Further, we assumed that probabilities to die or undergo re-intervention after events were comparable to existing heart valve substitutes. To assess long-term performance of TEHV, three aspects of their potential benefits were considered important: (1) Improved *durability* due to growth potential and lower rates of structural valve deterioration (SVD) and non-structural valve dysfunction resulting in longer time to re-intervention; (2) Reduced *thrombogenicity* resulting in lower rates of prosthetic valve thrombosis and reduced need for anticoagulation treatment; (3) Improved *infection resistance* resulting in lower rates of endocarditis and subsequent hospitalization and/or re-intervention.

Analyses

Cost-effectiveness analyses were performed from a healthcare perspective applying a 10-year time horizon with costs expressed in 2016 Euros and effects in QALYs. Future health benefits and costs were discounted with 1.5% and 4%, respectively, according to Dutch HTA guidelines.[16]

Several scenario analyses were performed to estimate the impact of variations in TEHV performance on costs, effects, and cost-effectiveness assuming that the price of TEHV is equal to that of existing heart valve substitutes (allograft/Contegra≈€5.000; other bioprostheses≈€2.500). First, we performed scenario analyses where performance components were varied separately with varying rates compared to existing heart valve substitutes. In the durability scenarios, the minimum durability of TEHV was 2.5, 5, 7.5, or 10 years. In the thrombogenicity and infection resistance scenarios, the occurrence of events was 25%, 50%, 75% and 100% less than with existing heart valve substitutes. Further, three scenario analyses where performance components of TEHV were varied simultaneously were performed. In the first combined scenario, we assumed *'perfect performance'* of TEHV in which the occurrence of prosthetic valve-related events was equal to the level in the general population (≈zero). In the second combined scenario, we assumed *'improved performance'* of TEHV in which the durability of TEHV was assumed to be ≥5 years and the rates of other prosthetic-valve related events were reduced with 50% compared to existing heart valve substitutes. In the final combined scenario, we assumed *'partial improved performance'* of TEHV in which occurrence of events related to thrombogenicity and infection resistance were reduced with 50%, but prosthetic valve dysfunction increased with 50% due to shorter durability than existing heart valve substitutes. In addition, subgroup analyses were performed for patients

aged ≤2 and >2 years for the 'improved performance' scenario. For all scenarios, we calculated the differences in costs and effects, and the incremental cost-effectiveness ratio (ICER; difference in costs divided by difference in effects) of RVOTR with TEHV compared to existing heart valve substitutes.

To reflect the uncertainty in input parameters of the patient-level simulation model (second-order uncertainty) and to describe what this means for uncertainty in outcomes, we performed probabilistic sensitivity analyses (PSA; Supplement 3). PSA was performed for the 'improved performance' scenario and was implemented as a double loop: an inner loop, in which 500 patients were sampled with replacement, and an outer loop in which 500 sets of input parameters of the model were randomly drawn (Supplement 3). For each set of input parameters, mean outcomes over all patients were recorded and the mean and credible interval (i.e. 2.5% and 97.5% percentile) over all 500 mean values for each outcome were calculated. PSA results were plotted in a cost-effectiveness plane reflecting the uncertainty around cost-effectiveness estimates.
To estimate the maximum price of TEHV to remain cost-effective compared to existing heart valve substitutes, the headroom was calculated. The headroom was calculated with the following formula: (difference in QALYs*cost-per-QALY threshold)+cost savings. The cost-per-QALY threshold was €20,000/QALY (Supplement 4).

Budget impact reflects the difference in total population-level costs of RVOTR with existing heart valve substitutes compared to TEHV. Budget impact analysis was performed for the 'improved performance' scenario for the first 10 years after introduction of TEHV. Differences in population-level costs were calculated by multiplying the differential total costs per patient with the expected number of candidates for RVOTR with TEHV, assuming substitution rates of 25%, 50%, 75% or 100% of existing heart valve substitutes by TEHV. The expected number of annual RVOTR candidates was assumed to be 85, based on the average number of patients who underwent RVOTR in the Netherlands in the years 2010-2013.[11]

RESULTS

Systematic review and meta-analysis of clinical outcomes

The systematic literature search identified 12,233 studies. After applying inclusion and exclusion criteria, 62 studies were included (Figure S2, references in Supplementary Material) encompassing 7,358 patients (age at surgery ≤2 years: n=1,270; >2 years: n=6,088) with a pooled mean follow-up of 6.1±3.5 years (Table 1).

Pooled estimates of patient and procedural characteristics, mortality, valve-related events and re-intervention risks and rates after RVOTR are presented in Table S1. Five-year survival was 86.5% and 85.7% and freedom from re-intervention was 46.1%, and 81.1%, in patients aged below and above 2 years, respectively (Figure 2). Mortality not directly related to valve-related events (i.e. background mortality and excess mortality) was 2.5 times higher after RVOTR in patients ≤2 years and 10 times higher after RVOTR in patients >2 years than in the general population (Supplement 5).

Table S3 presents the clinical input parameters of the patient-level simulation model derived from the meta-analyses. Early events besides stroke, re-exploration for bleeding, early RVOT re-intervention, valve thrombosis and endocarditis were reported too inconsistently and stroke and bleeding did not occur in any of the included studies and were therefore excluded from the analysis.

Table 1. Pooled estimates of patient characteristics and outcomes after RVOTR

	≤2 years			>2 years		
	Meta-analysis	**Included studies (n)**	**I^2, % ($\chi 2$ P-value)**	**Meta-analysis**	**Included studies (n)**	**I^2, % ($\chi 2$ P-value)**
Study characteristics						
No. of studies	19			37		
No. of patients	1270	19		6088	37	
Mean follow-up, years	8.0±3.8	22		5.7±3.5	41	
Patient and intervention characteristics						
Mean age, years	0.5±0.3	22		7.3±8.2	41	
Male	248 (51.4)	10		2110 (57.4)	28	
Mean weight, years	5.4±1.7	20		22.5±15.1	23	
Etiology		22			40	
TOF	183 (14.6)			2235 (42.5)		
TAC	836 (66.5)			687 (13.1)		
TGA	15 (1.2)			245 (4.7)		
TGA + VSD + PS	11 (0.9)			182 (3.5)		
DORV	13 (1.0)			159 (3.0)		
PS	2 (0.2)			97 (1.8)		
Previous cardiac intervention						
TOF repair	4 (7.7)	1		183 (40.3)	4	
Prior valved RVOTR	76 (23.8)	5		1122 (33.3)	22	
Palliative shunt	37 (24.3)	3		242 (22.8)	10	
Pulmonary valvuloplasty	4 (2.6)	3		50 (5.6)	8	
Valve prosthesis		19			37	
Allograft	836 (61.2)	19		2707 (42.1)	30	
Bioprosthesis	529 (38.7)	21		2590 (40.3)	34	
PTFE	-	16		1098 (17.1)	27	

Table 1. Continued

	≤2 years			>2 years		
	Meta-analysis	**Included studies (n)**	**I^2, % (χ2 P-value)**	**Meta-analysis**	**Included studies (n)**	**I^2, % (χ2 P-value)**
Early mortality and events, %						
Mortality	10.98 (8.19-14.70)	20	55 (0.002)	4.74 (3.42-6.56)	29	74 (0.000)
RVOT re-intervention	1.51 (0.54-4.28)	4	0 (0.768)	1.19 (0.48-2.98)	7	26 (0.227)
Re-exploration for bleeding	6.22 (1.10-35.11)	3	81 (0.005)	3.54 (1.70-7.37)	7	70 (0.003)
Stroke	-	0	-	1.69 (0.76-0.00)	3	0 (0.563)
Valve thrombosis	-	0	-	3.87 (0.77-19.36)	4	78 (0.003)
Endocarditis	1.80 (0.45-7.09)	2	0 (0.878)	-	1	-
Late events, %/year						
Structural valve deterioration	-	1	-	2.66 (1.06-6.69)	3	76 (0.014)
Non-structural valve dysfunction	-	0	-	0.60 (0.23-1.57)	2	33 (0.221)
Endocarditis	-	1	-	0.37 (0.20-0.68)	12	58 (0.006)
Thromboembolism	-	0	-	0.14 (0.05-0.41)	7	45 (0.092)
Valve thrombosis	-	0	-	0.11 (0.02-0.78)	2	0 (0.333)
Bleeding	-	0	-	-	1	-
Stroke	-	0	-	-	1	-
Re-intervention						
RVOT re-intervention, %/year	8.05 (5.44-11.90)	18	93 (0.000)	4.65 (3.67-5.88)	28	92 (0.000)
- Surgical, %	72.4	13		68.8	15	
- Percutaneous, %	27.6	13		31.2	15	
Conduit valve replacement, % of total re-interventions						
- Surgical, %	94.2	16		94.9	22	
- Percutaneous, %	2.6	7		26.7	9	
Late mortality, %/year						
Total mortality	1.39 (0.99-1.95)	19	44 (0.023)	0.75 (0.58-0.97)	33	59 (0.000)
Cardiac mortality	0.49 (0.27-0.86)	12	0 (0.876)	0.38 (0.27-0.53)	23	11 (0.311)
Valve-related mortality	0.59 (0.28-1.28)	11	0 (0.920)	0.28 (0.17-0.47)	23	27 (0.115)
Sudden unexplained death	0.45 (0.19-1.07)	10	0 (0.992)	0.14 (0.08-0.24)	22	0 (0.783)

Results are presented as n (%) or mean ± standard deviation. SD: standard deviation. TOF: Tetralogy of Fallot. TAC: truncus arteriosus communis. TGA: transposition of great arteries. VSD: ventricular septal defect. PS: pulmonary stenosis. DORV: double outlet right ventricle. RVOTR: right ventricular outflow tract reconstruction. RVOT: right ventricular outflow tract. PTFE: polytetrafluorethylene.

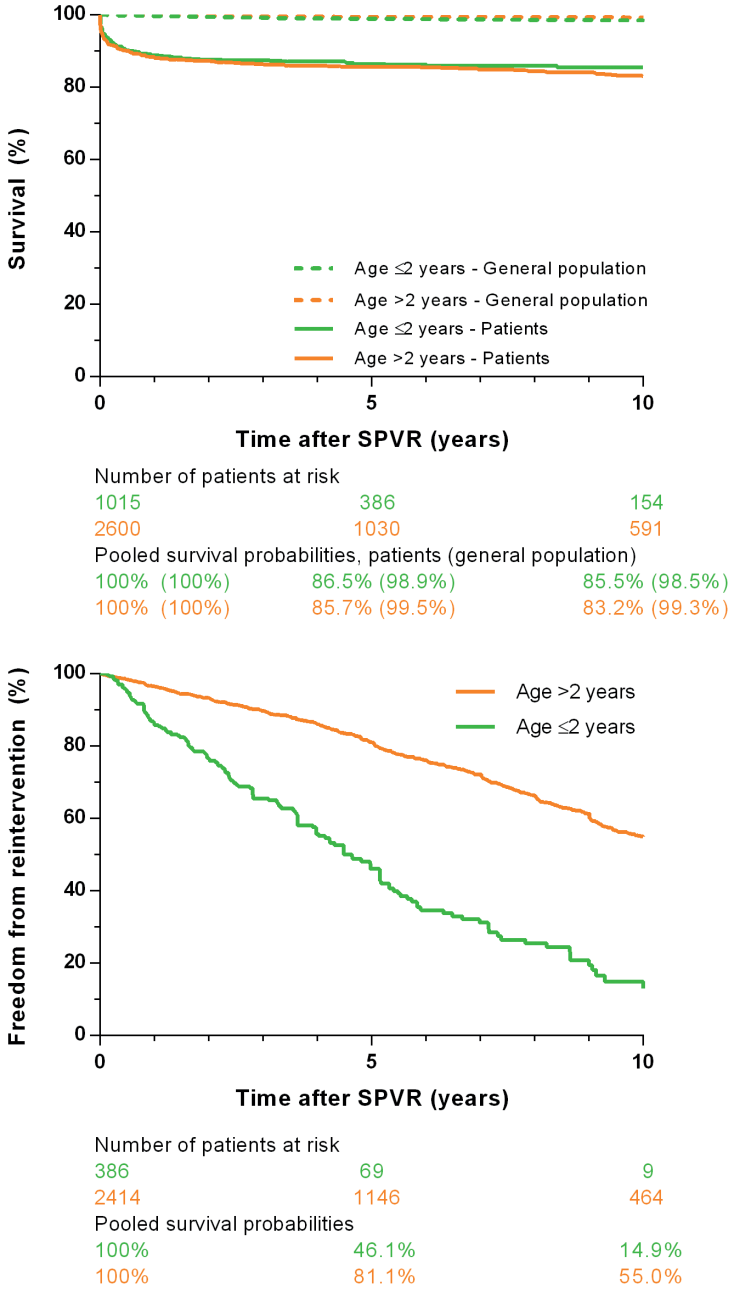


Figure 2. Pooled Kaplan-Meier survival and freedom from re-intervention (both surgical and percutaneous re-intervention) curves.

Survival curve of general population was based on weighted survival tables from Europe, United States, and Asia for the pooled median year of intervention among included studies(2001) at the same mean age and proportion of males imported in the microsimulation model with valve-related mortality and events set to zero.

Early Health Technology Assessment

Table 2 presents cost-effectiveness results of the scenario analyses. Of the three TEHV performance components, durability had the highest impact on cost-effectiveness. This is emphasized by results of the 'partial improved, scenario' where the consequences of reductions in durability of TEHV for the cost-effectiveness could not be offset by reduced thrombogenicity and improved infection resistance of TEHV. The 'perfect performance' scenario provides insight in the maximum QALY gain and cost savings of TEHV compared to existing heart valve substitutes: 0.107 QALYs and almost €21,000. In the 'improved performance' scenario, the assumed durability of TEHV of at least five years resulted in a reduction of occurrence of prosthetic valve dysfunction of 40%. In this scenario, RVOTR with TEHV resulted in a QALY gain of 0.058 and costs reduction of €10,378. Subgroup analyses showed QALY gains and cost reductions were higher in patients ≤2 years than in patients >2 years old at RVOTR (Table S6-7).

PSA of the 'improved performance' scenario showed that the difference in costs and effects varied, but all data points suggested QALY gains at lower costs (Figure 3). Consequently, the probability that the cost-effectiveness of TEHV would fall under the maximum cost-per-QALY was 100% for all thresholds.

Depending on improvements in clinical outcomes with TEHV, the price of TEHV can be higher while remaining cost-effective compared to existing heart valve substitutes. When applying a cost-per-QALY threshold of €20.000, this headroom varied from €12 if TEHV would only result in a small reduction in thrombogenicity to €23,041 if there would be no prosthetic valve related events at all using TEHV.

Figure 4/Table S8 shows that national cost savings in the next 10 years range from €1.9 million when 25% of RVOTR was performed with TEHV to €7.5 million when all RVOTR were performed with TEHV instead of existing heart valve substitutes.

Extensive internal validation was performed to check the model's performance using the TECH-VER checklist.[17] Further, Kaplan-Meier curves of survival and time to re-intervention derived from our meta-analysis that were used as input were comparable to curves derived from the model (Figures S3-4).

Table 2. Cost-effectiveness results of scenario analyses

	LY	QALYs	Costs	ΔLYs	ΔQALYs	ΔCosts	ICER	Headroom
Existing pulmonary valve substitutes	9.086	6.959	99,944					
Separate improvements in TEHV performance components*								
Durability								
No prosthetic valve dysfunction events	9.170	7.065	79,377	0.083	0.106	-20,568	TEHV dominates	22,688
Durability of TEHV≥7.5 years (-67% events)	9.163	7.055	85,017	0.076	0.096	-14,927	TEHV dominates	16,847
Durability of TEHV≥5 years (-40% events)	9.144	7.032	89,741	0.058	0.073	-10,203	TEHV dominates	11,673
Durability of TEHV≥2.5 years (-19% events)	9.117	6.994	94,254	0.031	0.036	-5,691	TEHV dominates	6,405
Thrombogenicity								
No VT events	9.086	6.959	99,901	0.000	0.000	-43	TEHV dominates	47
75% less VT events	9.086	6.959	99,911	0.000	0.000	-33	TEHV dominates	37
50% less VT events	9.086	6.959	99,922	0.000	0.000	-23	TEHV dominates	27
25% less VT events	9.086	6.959	99,934	0.000	0.000	-10	TEHV dominates	12
Infection resistance								
No endocarditis events	9.087	6.960	99,539	0.001	0.001	-406	TEHV dominates	428
75% less endocarditis events	9.087	6.959	99,655	0.001	0.001	-289	TEHV dominates	303
50% less endocarditis events	9.087	6.959	99,762	0.000	0.000	-183	TEHV dominates	193
25% less endocarditis events	9.087	6.959	99,832	0.000	0.000	-113	TEHV dominates	123
Combined improvements in TEHV performance components*								
Perfect performance (no prosthetic valve related events)	9.171	7.066	79,042	0.084	0.107	-20,903	TEHV dominates	23,041
Improved performance (durability ≥5 years and 50% less other prosthetic valve related events)	9.144	7.033	89,567	0.058	0.074	-10,378	TEHV dominates	11,856
Partial improved performance (decreased durability with 50%, 50% less other prosthetic valve related events)	8.976	6.931	123,741	-0.111	-0.028	23,796	Existing heart valve substitutes dominate	-24,356

LY: life years. QALY: quality adjusted life year. ICER: incremental cost-effectiveness ratio. TEHV: tissue-engineered heart valves. VT: valve thrombosis. Costs in Euros. *Results of subgroup analyses can be found in table S6-7.

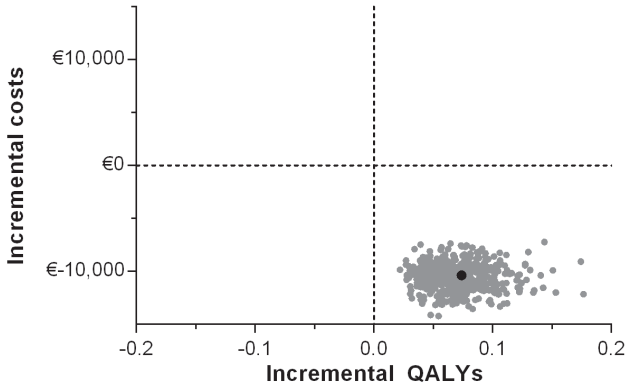


Figure 3. Probabilistic sensitivity analyses of RVOTR with TEHV ('improved performance' scenario) compared to existing heart valve substitutes.

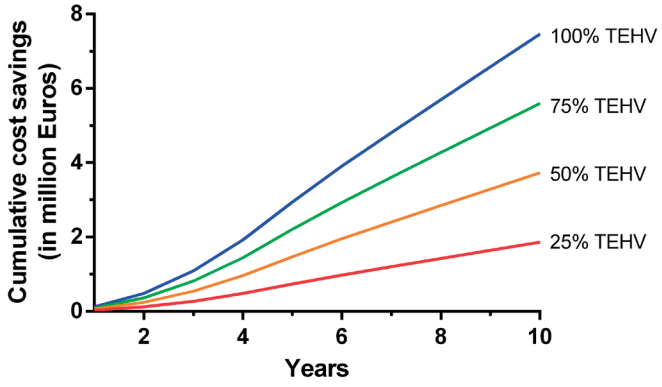


Figure 4. Cumulative cost savings in the first 10 years after introduction of RVOTR with TEHV ('improved performance' scenario) compared to existing heart valve substitutes.

DISCUSSION

In this study, we presented a virtual approach to assess the potential of the use of TEHV in children requiring RVOTR. The results of our meta-analysis indicated that there is room for improvement in the outcomes of existing pulmonary heart valve substitutes in children. If TEHV are associated with improved clinical outcomes, they are expected to be cost-effective compared to existing pulmonary heart valve substitutes in children. These results can be useful for different stakeholders.[10] First, this study informs patients and clinicians about expected outcomes after RVOTR with existing heart valve substitutes and potential outcomes of TEHV and therefore can support current and future treatment decision-making. Furthermore, raising awareness among clinicians about TEHV as future treatment option may result in faster adoption in clinical practice. [18] Second, our systematic review and meta-analysis of outcomes after RVOTR with existing heart valve substitutes informs biomedical developers about minimum performance requirements of TEHV. Furthermore, we showed that developers should especially aim at optimizing durability of TEHV, as this was associated with the highest QALY gains and cost savings. In children, the real durability issue with existing heart valve substitutes is the one of patients outgrowing their conduit. This is illustrated in this study by the low freedom from re-intervention in children who received a pulmonary valve substitute under 2 years of age. Considering the low occurrence rates of valve-related events in this patient group, this can only be explained by patients outgrowing their pulmonary valve substitute. Therefore, developers should focus on realizing the growth potential of TEHV. Depending on improvements in clinical outcomes, the price of TEHV can be higher than that of existing heart valve substitutes while remaining cost-effective. Finally, this study informs healthcare payers about potential upcoming market introduction of TEHV and its associated consequences for the healthcare budget, which may result in more timely decisions about reimbursement. [18] Although the annual number of children undergoing RVOTR in the Netherlands is small (85/year), large cost savings may be realized in the first decade after adoption of TEHV, varying from €1.9 million when 25% of RVOTR are performed with TEHV to €7.5 million when all RVOTR are performed with TEHV.

Inherent to any early Health Technology Assessment, we had to make assumptions regarding the costs and clinical performance of TEHV. Therefore, this study presents a theoretical exercise and the results are a prediction of the potential cost-effectiveness of TEHV. This also implies that, although this study was aimed at TEHV, our results can be applied to any new technology that will improve durability, reduce thrombogenicity, and/or decrease infection risk of existing pulmonary heart valve substitutes used for RVOTR in children. It is uncertain if and when TEHV will be introduced in clinical practice and whether the performance will indeed be improved compared to existing heart

valve substitutes. Preclinical and first-in-man clinical trials of tissue engineered heart valves and vascular grafts showed promising results and recently a small-scale first-in-man clinical trial of tissue-engineered pulmonary valved conduits for children with complex congenital heart disease was initiated.[6, 8] However, there are still several unresolved challenges regarding in-situ tissue engineering of heart valves, including finding the optimal material for the scaffold[19], the induction of regeneration of functional tissue[5], and finding the optimal balance between scaffold degradation and the formation of new tissue.[5]

This study has several limitations. First, relationships between occurrence rates of valve-related events after RVOTR on the one hand and patient and intervention characteristics and history of previous valve-related events on the other hand remains poorly defined and could, thus, not be incorporated in detail into our model. Instead, we used age subgroup-specific clinical input parameters to account for differences in these groups. Secondly, utility of patients after RVOTR was not based on patient-reported EQ-5D questionnaires in children. However, it is unlikely that possible inaccuracies in estimations of the start utility had a large impact on cost-effectiveness results because the start utility was equal for the intervention and comparator. Thirdly, we did not apply a lifetime horizon because of limited follow-up of clinical outcomes after RVOTR with children. Further extrapolation of clinical outcomes would lead to substantial uncertainty. However, it is expected that a longer time horizon would only reflect higher cost savings due to more prevented re-interventions in adulthood. Further, we could not perform external validation of the results because of unavailability of an external dataset on outcomes after RVOTR in children. Finally, this study was performed from a Dutch perspective and may therefore not be generalizable to countries with other health care systems.

In conclusion, this early HTA showed that TEHV developers should mainly focus on realizing the growth potential of TEHV because preventing patients from outgrowing their conduit and reducing the subsequent need for re-interventions was associated with the largest QALY gains and cost savings compared to existing heart valve substitutes in children requiring RVOTR. When biomedical developers succeed in realizing the growth potential, TEHV have the potential to be cost-effective compared to existing heart valve substitutes, commercially viable, and result in substantial savings for the national healthcare budget.

Funding. This work was supported by the Netherlands Cardio Vascular Research Initiative: The Dutch Heart Foundation, Dutch Federation of University Medical Centers, the Netherlands Organization for Health Research and Development and the Royal Netherlands Academy of Sciences.

Acknowledgements. We thank Wichor Bramer, information specialist at the Medical Library of the Erasmus University Medical Center, for his help with drafting the search query and executing the systematic literature retrieval.

Conflicts of interest. None.

REFERENCES

1. van der Linde, D., et al., *Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis.* Journal of the American College of Cardiology, 2011. **58**(21): p. 2241-2247.
2. The Society of Thoracic Surgeons (STS), *STS Congenital Heart Surgery Data Summary*. 2018, Duke Clinical Research Institute.
3. Oosterhof, T., M.G. Hazekamp, and B.J. Mulder, *Opportunities in pulmonary valve replacement.* Expert review of cardiovascular therapy, 2009. **7**(9): p. 1117-1122.
4. Yacoub, M.H. and J.J.M. Takkenberg, *Will heart valve tissue engineering change the world?* Nat Clin Pract Cardiovasc Med, 2005. **2**(2): p. 60-61.
5. Wissing, T.B., et al., *Biomaterial-driven in situ cardiovascular tissue engineering—a multi-disciplinary perspective.* NPJ Regenerative medicine, 2017. **2**(1): p. 18.
6. Kluin, J., et al., *In situ heart valve tissue engineering using a bioresorbable elastomeric implant–From material design to 12 months follow-up in sheep.* Biomaterials, 2017. **125**: p. 101-117.
7. Bouten, C.V., A. Smits, and F. Baaijens, *Can we Grow Valves Inside the Heart? Perspective on Material-based In Situ Heart Valve Tissue Engineering.* Frontiers in Cardiovascular Medicine, 2018. **5**: p. 54.
8. Bockeria, L.C., Thierry; Kim, Alex; Shatalov, Konstantin; Makarenko, Vladimir; Cox, Martijn; Svanidze, Oleg. *Polymeric bioabsorbable vascular graft in modified Fontan procedure - two-year follow-up*. in *7th World Congress of Pediatric Cardiology & Cardiac Surgery (WCPCCS)*. 2017. Barcelona.
9. Mokhles, M.M., S.A. Huygens, and M. Takkenberg, PhD, Johanna JM, *The risk in avoiding risk: Optimizing decision making in structural heart disease interventions.* Structural Heart, 2017: p. 1-7.
10. Huygens, S.A., et al., *Conceptual model for early health technology assessment of current and novel heart valve interventions.* Open Heart, 2016. **3**(2): p. e000500.
11. Huygens, S.A., et al., *How much does a heart valve implantation cost and what are the health care costs afterwards?* Open Heart, 2018. **5**(1).
12. Centraal Bureau voor de Statistiek (CBS). *Overlevingskansen; geslacht, leeftijd*. 2016 3-8-2017 [cited 2017 18-1-2018]; Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70701ned/table?ts=1517913558300.
13. Puvimanasinghe, J.P.A., et al., *Choice of a mechanical valve or a bioprosthesis for AVR: does CABG matter?* European Journal of Cardio-Thoracic Surgery, 2003. **23**(5): p. 688-695.
14. Organisation for Economic Co-operation and Development (OECD). *Expenditure by disease, age and gender under the System of Health Accounts (SHA) Framework : Current health spending by age*. 2011 [cited 2017.
15. Knowles, R.L., et al., *Patient-reported quality of life outcomes for children with serious congenital heart defects.* Archives of disease in childhood, 2014: p. archdischild-2013-305130.
16. Zorginstituut, N., *Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg.* Diemen: Zorginstituut Nederland, 2015.

17. Buyukkaramikli N.C, R.-v.M.M.P., Severens J.L.H, Al M. , *TECH-VER CHECKLIST: A Quality Assurance and Verification Checklist for the Technical Implementation of Health Economic Decision Analytic Models*. 2016, iMTA, Rotterdam, the Netherlands.
18. Buisman, L.R., et al., *The Early Bird Catches the Worm: Early Cost-Effectiveness Analysis of New Medical Tests.* International journal of technology assessment in health care, 2016: p. 1-8.
19. Motta SE, Lintas V, Fioretta ES, Hoerstrup SP, Emmert MY. Off-the-shelf tissue engineered heart valves for in situ regeneration: Current state, challenges and future directions. Expert review of medical devices 2018;15(1):35-45.
20. World Health Organization (WHO). *Global Health Observatory data repository - Life tables*. 2016 [cited 2017 7 April]; Available from: http://apps.who.int/gho/data/node.main.687?lang=en.
21. Arias, E., *United States Life Tables, 2001*. National Vital Statistics Reports, 2004. **52**(14): p. 39.

SUPPLEMENTAL MATERIAL

Supplement 1 - Methods systematic review and meta-analysis

This systematic review was conducted according to PRISMA guidelines[1] and registered in PROSPERO (CRD42016039674). On 2 May 2018, Embase, MEDLINE, The Cochrane Central, Google Scholar, and Web-Of-Science databases were searched by a biomedical information specialist using keywords regarding outcomes of pulmonary valve replacement (see end of this supplement). Titles and abstracts were independently screened by two reviewers (SH, JE). Inclusion criteria were observational studies or randomized controlled trials reporting on outcomes of isolated SPVR (max. 10% multiple valve replacement was allowed) of at least 20 patients with mean age≤12 and/or age range≤21 published in or after the year 2000. Studies were excluded if they exclusively enrolled patients with pre-existing comorbidities or certain prosthesis sizes, or only reported results of propensity matched study populations (because of less generalizability of the study population). In case of multiple publications on the same patient population, the publication with most follow-up patient-years and/or overall completeness of data was included. In case of disagreement between the reviewers, an agreement was negotiated.

Microsoft Office Excel 2011 was used for data extraction. Data extraction was performed independently by two researchers (SH, AN) and then jointly verified. Occurrence of valve-related events, re-intervention and mortality were documented according to the 2008 AATS/EACTS/STS guidelines.[2] Early outcome events were defined as occurring within the first 30 postoperative days, regardless of the patient's location. Late outcome events were defined as occurring after the first 30 postoperative days. If total follow-up duration in patient-years was not reported, it was calculated by multiplying the mean follow-up with the number of patients of that study.

Meta-analysis and heterogeneity tests were performed in Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA). Published Kaplan-Meier curves were digitized using Engauge Digitizer (version 10.3, http://markummitchell.github.io/engauge-digitizer). Shapiro-Wilk tests, extrapolation of estimated individual patient time-to-event data from the digitized curves, meta-analysis of the derived Kaplan-Meier curves were performed in R (version 3.3.2, R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria) using the software RStudio Version 1.0.136 (RStudio, Inc). Continuous variables are presented as mean±standard deviation. Categorical variables are presented as counts and percentages. Linearized event occurrence rates are presented as percentages per year. Pooled baseline patient characteristics were calculated with the use of sample size weighting. Early risks of

mortality and valve-related events and linearized occurrence rates of late mortality, valve-related events, and re-intervention were calculated for each individual study and pooled using the inverse variance method in a random-effects model. In the random-effects model the Der Simonian and Laird method was used for estimating the between studies variance.[3] Outcomes were pooled on a logarithmic scale, as the Shapiro–Wilk test revealed a significantly skewed distribution among the included studies in the majority of outcome measures. Inverse variance weighting was conducted according to the number of patients for early mortality and according to the number of follow-up patient-years for late events. In case an event was reported not to occur in an individual study, it was assumed that 0.5 patient experienced that event for the purpose of inverse variance weighting. The Cochrane-Q statistic and I^2 statistic were used to assess heterogeneity between studies.

Pooled Kaplan-Meier time-to-event meta-analysis was conducted by extrapolating and pooling estimates of individual patient time-to-event data from published Kaplan-Meier curves. Published Kaplan-Meier curves were digitized. An estimate of the individual patient time-to-event data was then extrapolated from the digitized curve coordinates, assuming a constant rate of censorship between each time point at which the number of patients at risk were specified.[4] If there were no Kaplan-Meier curves available, but time points of each event were reported or there were no events, the individual patient time-to-event data was manually reconstructed up to a maximum follow-up of the mean follow-up plus two standard deviations, under the same assumption of a constant rate of censorship. Reconstructed individual patient time-to-event data of each study were then combined.

Death due to non-valve related causes consists of background mortality in the general population and excess mortality not directly resulting from valve-related events. For estimation of the hazard ratios of the additional excess mortality not directly resulting from valve-related events relative to background mortality, the model containing only background mortality and mortality due to valve-related events (excluding early mortality) was run for 10,000 iterations at the mean age and proportion of males of the study population in the meta-analysis. The background mortality was obtained for the year 2016 in the Dutch general population.[5] Subsequently, the hazard ratios were estimated by fitting the survival output of this microsimulation model to the survival observed in our meta-analysis of time-to-event data (excluding early mortality) using varying values for the hazard ratio of excess mortality. The best fit was determined by using the least squares method.

Search terms

Embase.com

('pulmonary valve replacement'/de OR 'pulmonary valve prosthesis'/de OR 'Ross procedure'/de OR (('heart valve prosthesis'/de OR 'heart valve bioprosthesis'/exp OR 'heart valve replacement'/exp OR bioprosthesis/de OR xenograft/de OR allograft/de OR allotransplantation/de OR 'cardiovascular surgery'/de) AND ('pulmonary valve'/de OR 'pulmonary valve disease'/exp)) OR (((pulmon* OR lung) NEAR/6 (valv*) NEAR/6 (replace* OR transplant* OR allotransplant* OR allograft* OR homotransplant* OR homograft* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent* OR implant* OR substitut* OR conduit* OR melod* OR mechanical* OR insert*)) OR ((conduit OR reconstruct*) NEAR/15 (right OR pulm*) NEAR/6 (ventric* OR side*)) OR (reconstruct* NEAR/3 pulmon* NEAR/3 tract*) OR (rvot NEAR/3 reconstruct*) OR (Ross NEAR/3 (procedure* OR operation*)) OR (pulmonar* NEAR/3 autograft*) OR (((truncus NEAR/3 arteriosus) OR (common NEAR/3 arter* NEAR/3 trunk)) AND (correct* OR repair* OR reconstr*))):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) NOT ('case report'/de OR ((case NEXT/1 report*)):ab,ti)

Medline ovid

(((Heart Valve Prosthesis/ OR Heart Valve Prosthesis Implantation/ OR bioprosthesis/ OR heterograft/ OR allografts/ OR "Transplantation, Homologous"/ OR Cardiovascular Surgical Procedures/) AND (pulmonary valve/ OR Pulmonary Valve Insufficiency/ OR Pulmonary Valve Stenosis/ OR pulmonary artery/)) OR (((pulmon* OR lung) ADJ6 (valv*) ADJ6 (replace* OR transplant* OR allotransplant* OR allograft* OR homotransplant* OR homograft* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent* OR implant* OR substitut* OR conduit* OR melod* OR mechanical* OR insert*)) OR ((conduit OR reconstruct*) ADJ15 (right OR pulm*) ADJ6 (ventric* OR side*)) OR (reconstruct* ADJ3 pulmon* ADJ3 tract*) OR (rvot ADJ3 reconstruct*) OR (Ross ADJ3 (procedure* OR operation*)) OR (pulmonar* ADJ3 autograft*) OR (((truncus ADJ3 arteriosus) OR (common ADJ3 arter* ADJ3 trunk)) AND (correct* OR repair* OR reconstr*))).ab,ti.) NOT (exp animals/ NOT humans/) AND english.la. NOT (letter OR news OR comment OR editorial OR congresses OR abstracts). pt. NOT ("case reports"/ OR ((case ADJ report*)).ab,ti.)

Cochrane

((((pulmon* OR lung) NEAR/6 (valv*) NEAR/6 (replace* OR transplant* OR allotransplant* OR allograft* OR homotransplant* OR homograft* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent* OR implant* OR substitut* OR conduit* OR melod* OR mechanical* OR insert*)) OR ((conduit OR reconstruct*) NEAR/15 (right OR pulm*) NEAR/6 (ventric* OR side*)) OR

(reconstruct* NEAR/3 pulmon* NEAR/3 tract*) OR (rvot NEAR/3 reconstruct*) OR (Ross NEAR/3 (procedure* OR operation*)) OR (pulmonar* NEAR/3 autograft*) OR (((truncus NEAR/3 arteriosus) OR (common NEAR/3 arter* NEAR/3 trunk)) AND (correct* OR repair* OR reconstr*))):ab,ti) NOT (((case NEXT/1 report*)):ab,ti)

Web-of-science

TS=(((((pulmon* OR lung) NEAR/5 (valv*) NEAR/5 (replace* OR transplant* OR allotransplant* OR allograft* OR homotransplant* OR homograft* OR xenotransplant* OR xenograft* OR heterotransplant* OR heterograft* OR prosthe* OR bioprosthe* OR stent* OR implant* OR substitut* OR conduit* OR melod* OR mechanical* OR insert*)) OR ((conduit OR reconstruct*) NEAR/15 (right OR pulm*) NEAR/5 (ventric* OR side*)) OR (reconstruct* NEAR/2 pulmon* NEAR/2 tract*) OR (rvot NEAR/2 reconstruct*) OR (Ross NEAR/2 (procedure* OR operation*)) OR (pulmonar* NEAR/2 autograft*) OR (((truncus NEAR/3 arteriosus) OR (common NEAR/3 arter* NEAR/3 trunk)) AND (correct* OR repair* OR reconstr*)))) NOT (((case NEAR/1 report*)))) AND LA=(english) AND DT=(article)

Google scholar

"pulmonary valve replacement|transplantation|allotransplantation|allograft|homo-transplantation|homograft|xenotransplantation|xenograft|heterotransplantation|heter-ograft|prosthesis|bioprosthesis|implant|conduit"|"Ross procedure|operation"

References included studies

Allen, B.S., et al., *Pericardial tissue valves and Gore-Tex conduits as an alternative for right ventricular outflow tract replacement in children.* Ann Thorac Surg, 2002. **74**(3): p. 771-777.

Askovich, B., et al., *Right Ventricle-to-Pulmonary Artery Conduit Longevity: Is it Related to Allograft Size?* Ann Thorac Surg, 2007. **84**(3): p. 907-912.

Axelsson, I. and T. Malm, *Long-Term Outcome of Homograft Implants Related to Donor and Tissue Characteristics.* The Annals of Thoracic Surgery, 2018.

Aupècle, B., et al., *Intermediate follow-up of a composite stentless porcine valved conduit of bovine pericardium in the pulmonary circulation.* Ann Thorac Surg, 2002. **74**(1): p. 127-132.

Batlivala, S.P., et al., *Pulmonary valve replacement function in adolescents: A comparison of bioprosthetic valves and homograft conduits.* Ann Thorac Surg, 2012. **93**(6): p. 2007-2016.

Bell, D., et al., *Long-term performance of homografts versus stented bioprosthetic valves in the pulmonary position in patients aged 10-20 years.* European Journal of Cardio-Thoracic Surgery, 2018: p. 1-7.

Belli, E., et al., *The Performance of Hancock Porcine-Valved Dacron Conduit for Right Ventricular Outflow Tract Reconstruction.* Ann Thorac Surg, 2010. **89**(1): p. 152-158.

Benjacholamas, V., et al., *Bicuspidized pulmonary homograft for truncus arteriosus repair.* Asian Cardiovasc Thorac Ann, 2008. **16**(3): p. 189-193.

Bielefeld, M.R., et al., *Reoperative homograft right ventricular outflow tract reconstruction.* Ann Thorac Surg, 2001. **71**(2): p. 482-487; discussion 487-488.

Breymann, T., et al., *European Contegra multicentre study: 7-year results after 165 valved bovine jugular vein graft implantations.* Thorac Cardiovasc Surg, 2009. **57**(5): p. 257-269.

Brown, J.W., et al., *Performance of the CryoValve* SG human decellularized pulmonary valve in 342 patients relative to the conventional CryoValve at a mean follow-up of four years.* J Thorac Cardiovasc Surg, 2010. **139**(2): p. 339-348.

Chen, Q., et al., *Outcomes of surgical repair for persistent truncus arteriosus from neonates to adults: A single center's experience.* PLoS ONE, 2016. **11**(1).

Christenson, J.T., et al., *Homografts and xenografts for right ventricular outflow tract reconstruction: Long-term results.* Ann Thorac Surg, 2010. **90**(4): p. 1287-1293.

Cleuziou, J., et al., *Durability of down-sized homografts for the reconstruction of the right ventricular outflow tract.* Eur J Cardio-thorac Surg, 2016. **49**(5): p. 1421-1425.

Danton, M.H.D., et al., *Repair of truncus arteriosus: A considered approach to right ventricular outflow tract reconstruction.* Eur J Cardio-thorac Surg, 2001. **20**(1): p. 95-104.

Dittrich, S., et al., *Comparison of porcine xenografts and homografts for pulmonary valve replacement in children.* Ann Thorac Surg, 2000. **70**(3): p. 717-722.

Fiore, A.C., et al., *A Bovine Jugular Vein Conduit: A ten-year bi-institutional experience.* Ann Thorac Surg, 2011. **92**(1): p. 183-192.

Göber, V., et al., *Adverse mid-term outcome following RVOT reconstruction using the contegra valved bovine jugular vein.* Ann Thorac Surg, 2005. **79**(2): p. 625-631.

Hawkins, J.A., et al., *Simple versus complex truncus arteriosus: neutralization of risk but with increased resource utilization.* World J Pediatr Congenit Heart Surg, 2010. **1**(3): p. 285-291.

Hibino, N., et al., *Growth of diminutive central pulmonary arteries after right ventricle to pulmonary artery homograft implantation.* Ann Thorac Surg, 2014. **97**(6): p. 2129-2133.

Holmes, A., et al., *The Contegra conduit: Late outcomes in right ventricular outflow tract reconstruction.* Ann Pediatr Cardiol, 2012. **5**(1): p. 27-33.

Homann, M., et al., *Reconstruction of the RVOT with valved biological conduits: 25 Years experience with allografts and xenografts.* Eur J Cardio-thorac Surg, 2000. **17**(6): p. 624-630.

Hoxha, S., et al., *Twenty-Year Outcome After Right Ventricular Outflow Tract Repair Using Heterotopic Pulmonary Conduits in Infants and Children.* Artif Organs, 2016. **40**(1): p. 50-55.

Hunter, J., et al., *Assessment of the longevity of valves placed in the pulmonary position in patients with congenital heart disease.* Prog Pediatr Cardiol, 2016. **43**: p. 133-139.

Isomatsu, Y., et al., *Establishing right ventricle-pulmonary artery continuity by autologous tissue: an alternative approach for prosthetic conduit repair.* Ann Thorac Surg, 2004. **78**(1): p. 173-180.

Kalfa, D.M., et al., *Pulmonary position cryopreserved homograft in non-Ross patients: How to improve the results?* Eur J Cardio-thorac Surg, 2012. **42**(6): p. 981-987.

Karamlou, T., et al., *Oversizing pulmonary homograft conduits does not significantly decrease allograft failure in children.* Eur J Cardio-thorac Surg, 2005. **27**(4): p. 548-553.

Kim, W.H., et al., *Follow-Up of Shelhigh Porcine Pulmonic Valve Conduits.* Ann Thorac Surg, 2007. **84**(6): p. 2047-2050.

Kim, H.W., et al., *Long term results of right ventricular outflow tract reconstruction with homografts.* Korean j. thorac. cardiovasc. surg., 2011. **44**(2): p. 108-114.

Kim, Y.J., et al., *Ventricular outflow tract reconstruction with polystan valved conduit.* Asian Cardiovasc Thorac Ann, 2001. **9**(3): p. 187-191.

Koh, M., et al., *Long-term outcome of right ventricular outflow tract reconstruction using a handmade trileaflet conduit.* Eur J Cardio-thorac Surg, 2005. **27**(5): p. 807-814.

Koirala, B., et al., *Extending the usable size range of homografts in the pulmonary circulation: Outcome of bicuspid homografts.* Ann Thorac Surg, 2002. **73**(3): p. 866-870.

Kreutzer, C., et al., *The autologous pericardial valved conduit for right ventricular outflow tract reconstruction.* Oper Tech Thorac Cardiovasc Surg, 2003. **8**(3): p. 146-149.

Louis, C., et al., *Modified Repair of Type I and II Truncus Arteriosus Limits Early Right Ventricular Outflow Tract Reoperation.* Semin Thoracic Surg, 2018.

Lun, K.S., et al., *Intermediate-term results of repair of congenital heart diseases using pulmonary homografts.* Hong Kong J Paediatr, 2005. **10**(4): p. 271-281+313.

Lund, A.M., et al., *Early re-intervention on the pulmonary arteries and right ventricular outflow tract after neonatal or early infant repair of truncus arteriosus using homograft conduits.* Am J Cardiol, 2011. **108**(1): p. 106-113.

McElhinney, D.B., et al., *Re-interventions after repair of common arterial trunk in neomates and young infants.* J Am Coll Cardiol, 2000. **35**(5): p. 1317-1322.

McMullan, D.M., et al., *Evaluation of downsized homograft conduits for right ventricle-to-pulmonary artery reconstruction.* J Thorac Cardiovasc Surg, 2006. **132**(1): p. 66-71.

Mercer, C.W., et al., *Polytetrafluoroethylene conduits versus homografts for right ventricular outflow tract reconstruction in infants and young children: An institutional experience.* J Thorac Cardiovasc Surg, 2018. **155**(5): p. 2082-2091.e1.

Mery, C.M., et al., *Risk factors for development of endocarditis and re-intervention in patients undergoing right ventricle to pulmonary artery valved conduit placement.* J Thorac Cardiovasc Surg, 2016. **151**(2): p. 432-439, 441.e431-432.

Naimo, P.S., et al., *Outcomes of Truncus Arteriosus Repair in Children: 35 Years of Experience From a Single Institution.* Semin Thorac Cardiovasc Surg, 2016. **28**(2): p. 500-511.

Ootaki, Y., et al., *Medium-Term Outcomes After Implantation of Expanded Polytetrafluoroethylene Valved Conduit.* Ann Thorac Surg, 2017.

Pratap, H., et al., *Right ventricular outflow tract reconstruction using Contegra® conduit in Tetralogy of Fallot: single centre experience.* 2010. **0**: p. 1-4.

Prior, N., et al., *Bovine jugular vein valved conduit: Up to 10 years follow-up.* J Thorac Cardiovasc Surg, 2010. **0**.

Rastan, A.J., et al., *Bovine Jugular Vein Conduit for Right Ventricular Outflow Tract Reconstruction: Evaluation of Risk Factors for Mid-Term Outcome.* Ann Thorac Surg, 2006. **82**(4): p. 1308-1315.

Ruzmetov, M., et al., *Does the Homograft for RVOT Reconstruction in Ross: Patients Fare Better than for Non-Ross Patients? A Single-Center Experience.* J Heart Valve Dis, 2015. **24**(4): p. 478-483.

Saritas, B., et al., *Early surgical outcome of pulmonary valve replacement in patients with previous right ventricle outflow tract reconstruction.* Turk Gogus Kalp Damar Cerrahisi Derg., 2017. **25**(3): p. 363-367.

Sfyridis, P.G., et al., *The contegra® valved heterograft conduit for right ventricular outflow tract reconstruction: A reliable solution.* Hell J Cardiol, 2011. **52**(6): p. 501-508.

Shebani, S.O., et al., *Right ventricular outflow tract reconstruction using Contegra® valved conduit: Natural history and conduit performance under pressure.* Eur J Cardio-thorac Surg, 2006. **29**(3): p. 397-405.

Shinkawa, T., et al., *Outcome of right ventricle to pulmonary artery conduit for biventricular repair.* Ann Thorac Surg, 2015. **99**(4): p. 1357-1366.

Shinkawa, T., et al., *Valved Polytetrafluoroethylene Conduits for Right Ventricular Outflow Tract Reconstruction.* Ann Thorac Surg, 2015. **100**(1): p. 129-137.

Sinzobahamvya, N., et al., *Survival and re-intervention after neonatal repair of truncus arteriosus with valved conduit.* Eur J Cardio-thorac Surg, 2008. **34**(4): p. 732-737.

Tatebe, S., et al., *Right Ventricle to Pulmonary Artery Reconstruction Using a Valved Homograft.* Circ J, 2003. **67**(11): p. 906-912.

Thompson, L.D., et al., *Neonatal repair of truncus arteriosus: Continuing improvement in outcomes.* Ann Thorac Surg, 2001. **72**(2): p. 391-395.

Tierney, E.S.S., et al., *Pulmonary position cryopreserved homografts: Durability in pediatric Ross and non-Ross patients.* J Thorac Cardiovasc Surg, 2005. **130**(2): p. 282-286.

Tiete, A.R., et al., *Right ventricular outflow tract reconstruction with the Contegra bovine jugular vein conduit: A word of caution.* Ann Thorac Surg, 2004. **77**(6): p. 2151-2156.

Tweddell, J.S., et al., *Factors affecting longer of homograft valves used in right ventricular outflow tract reconstruction for congenital heart disease.* Circulation, 2000. **102**(19): p. III130-III135.

Urso, S., et al., *Evolution of the Z-score in size-reduced bicuspid homografts.* J Heart Valve Dis, 2012. **21**(4): p. 521-526.

Vitanova, K., et al., *Which type of conduit to choose for right ventricular outflow tract reconstruction in patients below 1 year of age?+.* Eur J Cardiothorac Surg, 2014. **46**(6): p. 961-966; discussion 966.

Vohra, H.A., et al., *Long-term follow-up after primary complete repair of common arterial trunk with homograft: a 40-year experience.* J Thorac Cardiovasc Surg, 2010. **140**(2): p. 325-329.

Yamagishi, M., *Right Ventricular Outflow Reconstruction Using a Polytetrafluoroethylene Conduit With Bulging Sinuses and Tricuspid Fan-shaped Polytetrafluoroethylene Valve.* Oper Tech Thorac Cardiovasc Surg, 2016. **21**(3): p. 211-229.

Yamashita, E., et al., *Smaller-Sized Expanded Polytetrafluoroethylene Conduits With a Fan-Shaped Valve and Bulging Sinuses for Right Ventricular Outflow Tract Reconstruction.* Ann Thorac Surg, 2016. **102**(4): p. 1336-1344.

Supplement 2 – Utility of patients after RVOTR

Utility of patients after RVOTR without complications was based on patient-reported quality of life measured with the Pediatric Quality of Life Inventory (PedsQL) of children with serious congenital heart defects in the United Kingdom.[6] The median quality of life score in children with congenital heart diseases was 11% lower than their healthy classmates.[6] This relative difference was applied to the utility of young adults in the general population[7] (because EQ-5D utilities of children were not available), resulting in an utility of 0.852 in children after RVOTR.

Supplement 3 – Probabilistic sensitivity analyses

To estimate the numbers of patients and simulations required in our probabilistic sensitivity analyses (PSA), we used the approach described in O'Hagan et al. as recommended by the NICE DSU guidelines on patient-level modelling.[8] In this approach the number of PSA runs (outer loop = N) and patients per PSA run (inner loop = n) needed to achieve accurate cost-effectiveness estimates while keeping the number of runs as small as possible can be estimated. The cost-effectiveness measure used in this estimation was the number of undiscounted QALYs.

The box below showed the approximations presented by O'Hagan et al. that we used. According to O'Hagan et al. the approximations are sufficiently accurate when k is at least 25 and c is less than or equal to 0.2.

M = 8k/c2 = N*n
n = 1 + k

N = number of PSA runs (outer loop)
n = number of patients per PSA run (inner loop)
k = patient-level variance / parameter variance
c = coefficient of variance = SD parameter / mean of parameter

The patient-level variance was 5.78, estimated with a deterministic run of 25,000 patients. The parameter variance was 0.16, which was the mean of 500 model runs each of them based on 100 patients. Therefore, k was 5.78 / 0.16 = 35. Based on the formulas described above the number of patients per PSA run would be 35 + 1 = 36 (after rounding up). Assuming a c of 0.2, M = 7,070 and the number of PSA runs would be 195 (after rounding up). However, the choice of c = 0.2 was arbitrary and based on the minimum accuracy requirement and there is no generally accepted threshold value for c in the literature. Therefore, we chose to run the 500 PSA runs including 500 patients each, translating to a value for c of approximately 0.12 (i.e. almost twice more accurate).

Supplement 4 – Cost-per-QALY threshold

Methods

In the Netherlands, the cost-per-QALY threshold depends on disease burden of patients with current standard of care; the higher the disease burden, the higher the cost-per-QALY threshold.[9] Disease burden was expressed in proportional shortfall (i.e. fraction of QALYs that people lose relative to their remaining life expectancy) which can take a value between 0 (minimal burden of disease) and 1 (maximum burden of disease) and was calculated with the iMTA Disease Burden Calculator (iDBC) v1.3.[10, 11] The expected QALYs of children after RVOTR with existing heart valve substitutes was calculated by applying a lifetime horizon in our patient-level simulation model.

Results

Children who undergo RVOTR with existing heart valve substitutes can expect 48 QALYs, compared to 69 QALYs in the general population. Hence, 21 QALYs are lost due to the condition with standard care (31% of normal QALY expectancy), translating

to a disease burden of 0.31. For a disease burden below 0.41 the appropriate cost-effectiveness threshold is €20,000/QALY in the Netherlands.[12]

Supplement 5 – Excess mortality

For estimation of the hazard ratios of the additional excess mortality not directly resulting from valve-related events relative to background mortality, the model containing only background mortality and mortality due to valve-related events (excluding early mortality) was run for 10,000 iterations at the mean age and proportion of males of the pooled KM survival curve from our meta-analysis. Subsequently, the hazard ratios were estimated by fitting the survival output of this simulation model to the pooled KM survival (excluding early mortality) using varying values for the hazard ratio of excess mortality. The best fit was determined by using the least squares method (Table below).

Least squares regression of modeled survival vs. observed survival for estimation of excess mortality not directly related to valve-related events.

	Age at intervention ≤ 2	Age at intervention > 2
Hazard ratio[1]	**Sum of squared residuals[2]**	**Sum of squared residuals[2]**
1.0	229	1617
2.0	71	
2.5	**55**	
3.0	67	
9.0		135
10.0		**118**
11.0		138

Bold print indicates the selected model. [1]Hazard ratio of background mortality + excess mortality relative to background mortality. [2]Sum of squared residuals between microsimulation-based survival and survival observed in our meta-analysis of Kaplan-Meier freedom from all-cause mortality.

Table S1. Baseline characteristics of patient populations

BASELINE CHARACTERISTICS	All patients (n=338)	Age <2 years (n=198)	Age ≥ 2 years (n=140)
Patient related			
Age, mean±SD (range)	4.5±5.8 (0.0-18.0)	0.5±0.4 (0.0-1.8)	10.3±4.9 (2.0-18.0)
Sex (%)	200 (59.2)	116 (58.6)	84 (60.0)
Socioeconomic status (SES, in quartiles) (%)			
0-20	57 (16.9)	35 (17.7)	22 (15.7)
21-40	71 (21.0)	39 (19.7)	32 (22.9)
41-70	103 (30.5)	57 (28.8)	46 (32.9)
71-100	107 (31.7)	67 (33.8)	40 (28.6)
Procedure related			
Concomitant TOF repair (%)	187 (55.3)	171 (86.4)	16 (11.4)

TOF: Tetralogy of Fallot.

Table S2. Definitions of parameters

BASELINE CHARACTERISTICS	
Patient related	
Age	Continious
Sex	Male = 1; female = 0
Socioeconomic status	Based on status scores reflecting the SES of a district (defined by postal code) based on characteristics of its residents: education, income, and position on the labor market. The status scores were divided in four groups based on percentiles, with lower percentiles representing lower SES.
Procedure related	
Concomitant TOF repair	TOF repair procedure that is performed at the same time of the valve replacement.
INTERMEDIATE OUTCOMES	
Stroke	Stroke with or without residual injury.
Vascular complication*	All arterial vascular complications, such as dissection of the aorta, acute ischemia of the arm or leg due to vascular problems, IABP complications, etc.
Bleeding	Any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g., vision loss) or necessitates transfusion.[2]
Prosthetic valve dysfunction	Structural valve deterioration and non-structural valve dysfunction
- Structural valve deterioration (SVD)	Dysfunction or deterioration involving the operated valve (exclusive of infection or thrombosis), referring to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components of a prosthetic valve.[2]
- Non-structural valve dysfunction (NSVD)	Any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the operated valve or hemolysis.[2]
Prosthetic valve thrombosis	Any thrombus not caused by infection attached to or near an operated valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment.[2]
Prosthetic valve endocarditis	Any infection involving a prosthetic valve.[2]
Re-intervention	Any surgical or transcatheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted prosthesis.[2]

*Events are only included during the first 30 days after the intervention.

Table S3. Input parameters patient-level simulation model

	≤2 years	Distribution	>2 years	Distribution	Source
Clinical outcomes					
Early mortality, %					
After initial intervention	11.0	Beta (α 39; β 316)	4.7	Beta (α 32; β 640)	Meta-analysis
After surgical re-intervention	2.6	Beta (α 8; β 308)	2.6	Beta (α 8; β 308)	[13-15]
After percutaneous re-intervention	0.4	Beta (α 1; β 240)	0.4	Beta (α 1; β 240)	Meta-analysis
Early events, %					
Stroke	0.0	-	1.7	Beta (α 5; β 299)	Meta-analysis
Bleeding	6.2	Beta (α 0.4; β 6)	3.5	Beta (α 6; β 153)	Meta-analysis
Prosthetic valve dysfunction	1.5	Beta (α 2; β 160)	1.2	Beta (α 3; β 287)	Meta-analysis
Prosthetic valve thrombosis	0.0	-	3.9	Beta (α 1; β 15)	Meta-analysis
Prosthetic valve endocarditis	1.8	Beta (α 1; β 59)	0.0	-	Meta-analysis
Late events, %/year±SD					
Prosthetic valve dysfunction	shape 1.23±0.07; scale 5.94±0.38	Weibull	shape 1.19±0.03; scale 17.18±0.61	Weibull	Meta-analysis
Probability of dying(%)	0.0	-	0.0	-	Assumption Meta-analysis
Probability of surgical re-intervention(%) (replacement of pulmonary valve prosthesis)	72.4	Beta (α 246; β 94)	68.8	Beta (α 537; β 243)	
Probability of percutaneous re-intervention(%) (balloon dilation of pulmonary valve)	27.6		31.2		
Prosthetic valve thrombosis	0.0	-	0.1±0.2	Lognormal	Meta-analysis
Probability of dying(%)	-	-	0.0	Dirichlet[4] (α^1 0; α^2 3; α^3 23)	Assumption [16]
Probability of re-intervention(%)	-	-	12.0		
Prosthetic valve endocarditis	0.0	-	0.4±0.1	Lognormal	Meta-analysis
Probability of dying(%)	-	-	0.0	Dirichlet[4] (α^1 0; α^2 21; α^3 9)	Meta-analysis
Probability of re-intervention(%)	-	-	70.0		
Hazard ratio excess mortality	2.5	Uniform (-/+10%)	10.0	Uniform (-/+10%)	Meta-analysis
Costs	**All children**	**Distribution**			**Source**
Intervention costs					
RVOTR	22,068	Multivariate normal[3]			[17]*

	All children		Distribution			Source
Event treatment costs						
Stroke	1,435		Multivariate normal[3]			[17]*
Reexploration for bleeding	5,048		Multivariate normal[3]			[18]
Bleeding	1,617		Multivariate normal[3]			[18]
Prosthetic valve dysfunction[1]	7,524		Multivariate normal[3]			[19]
Prosthetic valve thrombosis[1]	5,824		Multivariate normal[3]			[20-22]
Prosthetic valve endocarditis[1]	8,069		Multivariate normal[3]			[17]*
Re-intervention RVOTR	20,303		Multivariate normal[3]			[17]*
Other healthcare costs[2]						
Postintervention year 1	11,910		Multivariate normal[3]			[17]*
Postintervention year 2	5,562		Multivariate normal[3]			[17]*
Postintervention year 3	5,077		Multivariate normal[3]			[17]*
Utilities	**All children**		**Distribution**			
Utilities at start of the simulation						
RVOTR	0.852		Uniform (-/+ 10%)			[6, 7]
Utilities after events	**Utility multiplier**	**Duration**				
Stroke	0.841	Lifetime	Uniform[5]			[23, 24]
Vascular complications	0.981	1 week	Uniform[5]			[25]
Bleeding	0.965	1 year	Uniform[5]			[26]
Prosthetic valve dysfunction	0.886[1]	Lifetime	Uniform[5]			[27, 28]
Prosthetic valve thrombosis	0.968[1]	10 days	Uniform[5]			[20, 29]
Prosthetic valve endocarditis	0.968[1]	6 weeks	Uniform[5]			[29, 30]
Re-intervention	0.946	Lifetime	Uniform[5]			Assumption

SD: standard deviation. RVOTR: right ventricular outflow tract reconstruction. Costs are reported in 2010-2013 Euros, but are adjusted to 2016 price level in the model. *Mean in the Vektis database. Costs in the model dependent on patient and intervention characteristics using (M)GLM. [17]
[1]Conservative treatment, no re-intervention. [2]Mean total healthcare costs per year including costs of treatment of events and death (costs types are estimated separately in the model), but excluding intervention costs. [3]Multivariate normal distribution: coefficients of the regression model are randomly drawn from a multivariate normal distribution based on coefficients and variance-covariance matrix. [4]Dirichlet distribution parameters: α^1 = number of deaths, α^2 = number of re-interventions, α^3 = number of other treatment. [5]50% deviation of 1-utility multiplier to prevent the utility multiplier from exceeding 1.

Table S4. Specification of type of equation per outcome

Equation number	Outcome	Type of equation	Source
1	Intervention costs	Generalized linear model with gamma distribution and identity link (PROC GENMOD in SAS) Intervention costs = valve position + concomitant procedures + age group + male gender + co-morbidity category + SES class + death within 6 months after the intervention.	[17]
2	Event costs (AKI, AF, stroke, MI, PI, re-intervention)	Generalized linear model with gamma distribution and identity link (PROC GENMOD in SAS) Event costs = age group + male gender + co-morbidity category + SES class + death within 6 months after the complication.	[17]
3	Other healthcare costs	Multilevel generalized linear model for with normal distribution and identity link (PROC GLIMMIX in SAS) Other healthcare costs adults = time since intervention + death + age group at intervention + male gender + SES class + AF + AKI + stroke + TIA + endocarditis + MI + PI + re-intervention. Other healthcare costs children = time since intervention + male gender + SES class.	Table S5 [17]

SES: socioeconomic status. AKI: acute kidney injury. AF: atrial fibrillation. MI: myocardial infarction. PI: pacemaker implantation. TIA: transient ischemic attack.

Table S5. Multilevel generalized linear model for the other annual healthcare costs after surgical valve replacement in postintervention years 1 through 4.

Other healthcare costs		Children (n=411)	
Parameter	**β**	**95% CI**	**P-value**
Intercept	16,216	-36,911-69,343	0.550
Time (compared to year 1 excluding intervention costs)			
Year 2	-10,922	-66,703-44,859	0.700
Year 3	-14,256	-66,584-38,073	0.590
Year 4	-5,316	-63,559-52,926	0.860
Male	1,006	-30,500-32,513	0.950
SES[1] (compared to highest SES: 71-100)			
0-20	8,208	-36,553-52,968	0.720
21-40	2,731	-41,217-46,679	0.900
41-70	1,922	-37,627-41,472	0.920

CI: confidence interval. SES: socioeconomic status. [1]Higher percentiles represent higher SES.

Table S6. Cost-effectiveness results of scenario analyses in patients ≤2 years old at the time of surgery

	LY	QALYs	Costs	ΔLYs	ΔQALYs	ΔCosts	ICER	Headroom
SPVR with current valve prostheses	8.793	6.814	105,005					
Improved durability of TEHV								
No prosthetic valve dysfunction events	8.905	6.966	77,573	0.112	0.152	-27,432	TEHV dominates	30,468
Durability of TEHV ≥7.5 years (-66% events)	8.895	6.952	85,319	0.102	0.138	-19,685	TEHV dominates	22,453
Durability of TEHV ≥5 years (-30% events)	8.869	6.920	91,433	0.076	0.106	-13,572	TEHV dominates	15,688
Durability of TEHV ≥2.5 years (-20% events)	8.834	6.864	97,079	0.041	0.051	-7,926	TEHV dominates	8,936
Improved thrombogenicity of TEHV								
No VT events	8.793	6.814	104,979	0.000	0.000	-26	TEHV dominates	28
75% less VT events	8.793	6.814	104,984	0.000	0.000	-20	TEHV dominates	20
50% less VT events	8.793	6.814	104,989	0.000	0.000	-16	TEHV dominates	16
25% less VT events	8.793	6.814	104,999	0.000	0.000	-6	TEHV dominates	8
Improved infection resistance of TEHV								
No endocarditis events	8.794	6.815	104,794	0.001	0.001	-211	TEHV dominates	227
75% less endocarditis events	8.793	6.814	104,855	0.001	0.001	-149	TEHV dominates	161
50% less endocarditis events	8.793	6.814	104,902	0.000	0.000	-102	TEHV dominates	110
25% less endocarditis events	8.793	6.814	104,943	0.000	0.000	-62	TEHV dominates	64

LY: life years. QALY: quality adjusted life year. ICER: incremental cost-effectiveness ratio. TEHV: tissue-engineered heart valves. VT: valve thrombosis. Costs in Euros.

Table S7. Cost-effectiveness results of scenario analyses in patients >2 years old at the time of surgery

	LY	QALYs	Costs	ΔLYs	ΔQALYs	ΔCosts	ICER	Headroom
SPVR with current valve prostheses	9.485	7.149	93,035					
Improved durability of TEHV								
No prosthetic valve dysfunction events	9.525	7.187	82,061	0.040	0.038	-10,975	TEHV dominates	11,729
Durability of TEHV ≥7.5 years (-71% events)	9.522	7.182	84,755	0.037	0.034	-8,280	TEHV dominates	8,950
Durability of TEHV ≥5 years (-44% events)	9.514	7.174	87,431	0.029	0.025	-5,604	TEHV dominates	6,104
Durability of TEHV ≥2.5 years (-19% events)	9.500	7.161	90,108	0.015	0.012	-2,928	TEHV dominates	3,176
Improved thrombogenicity of TEHV								
No VT events	9.485	7.149	92,960	0.000	0.000	-75	TEHV dominates	79
75% less VT events	9.485	7.149	92,979	0.000	0.000	-56	TEHV dominates	60
50% less VT events	9.485	7.149	92,997	0.000	0.000	-38	TEHV dominates	42
25% less VT events	9.485	7.149	93,017	0.000	0.000	-18	TEHV dominates	18
Improved infection resistance of TEHV								
No endocarditis events	9.487	7.151	92,355	0.002	0.002	-681	TEHV dominates	725
75% less endocarditis events	9.486	7.150	92,546	0.001	0.001	-489	TEHV dominates	509
50% less endocarditis events	9.486	7.150	92,719	0.001	0.001	-317	TEHV dominates	329
25% less endocarditis events	9.486	7.150	92,847	0.001	0.001	-188	TEHV dominates	212

LY: life years. QALY: quality adjusted life year. ICER: incremental cost-effectiveness ratio. TEHV: tissue-engineered heart valves. VT: valve thrombosis. Costs in Euros.

Table S8. Cumulative cost savings per year in the first 10 years after introduction of TEHV with varying substitution rates

	SPVR (n=85/year)			
Substitution rate TEHV	25%	50%	75%	100%
Years				
1	30,768	61,536	92,304	123,073
2	120,965	241,931	362,896	483,862
3	272,888	545,776	818,664	1,091,552
4	480,405	960,810	1,441,215	1,921,621
5	735,658	1,471,316	2,206,974	2,942,632
6	976,867	1,953,735	2,930,602	3,907,470
7	1,203,281	2,406,562	3,609,843	4,813,124
8	1,424,670	2,849,340	4,274,009	5,698,679
9	1,646,096	3,292,193	4,938,289	6,584,386
10	1,866,627	3,733,254	5,599,882	7,466,509

SPVR: surgical pulmonary valve replacement. TEHV: tissue-engnieered heart valves. Costs in Euros.

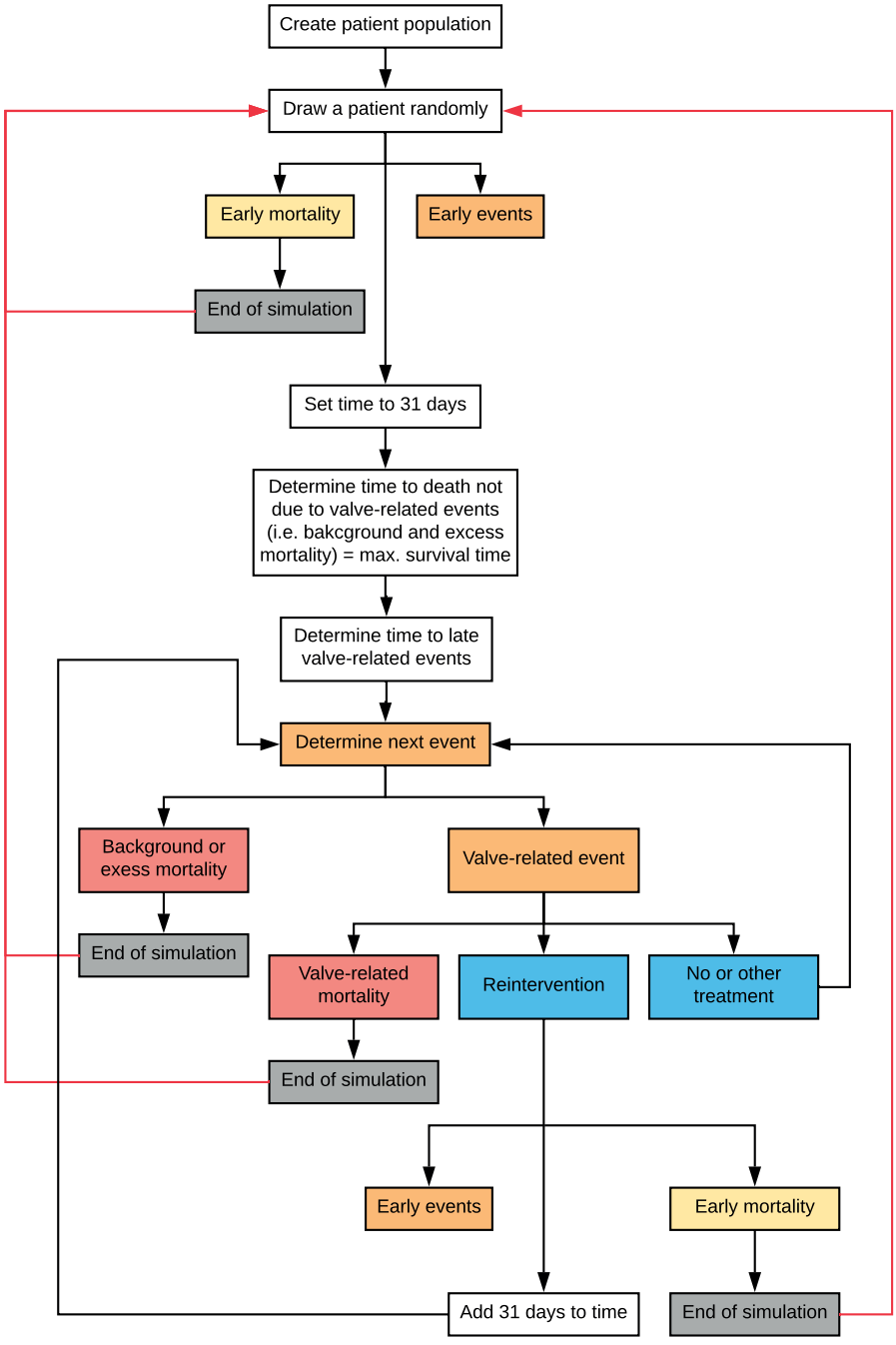


Figure S1. Flowchart patient level simulation model

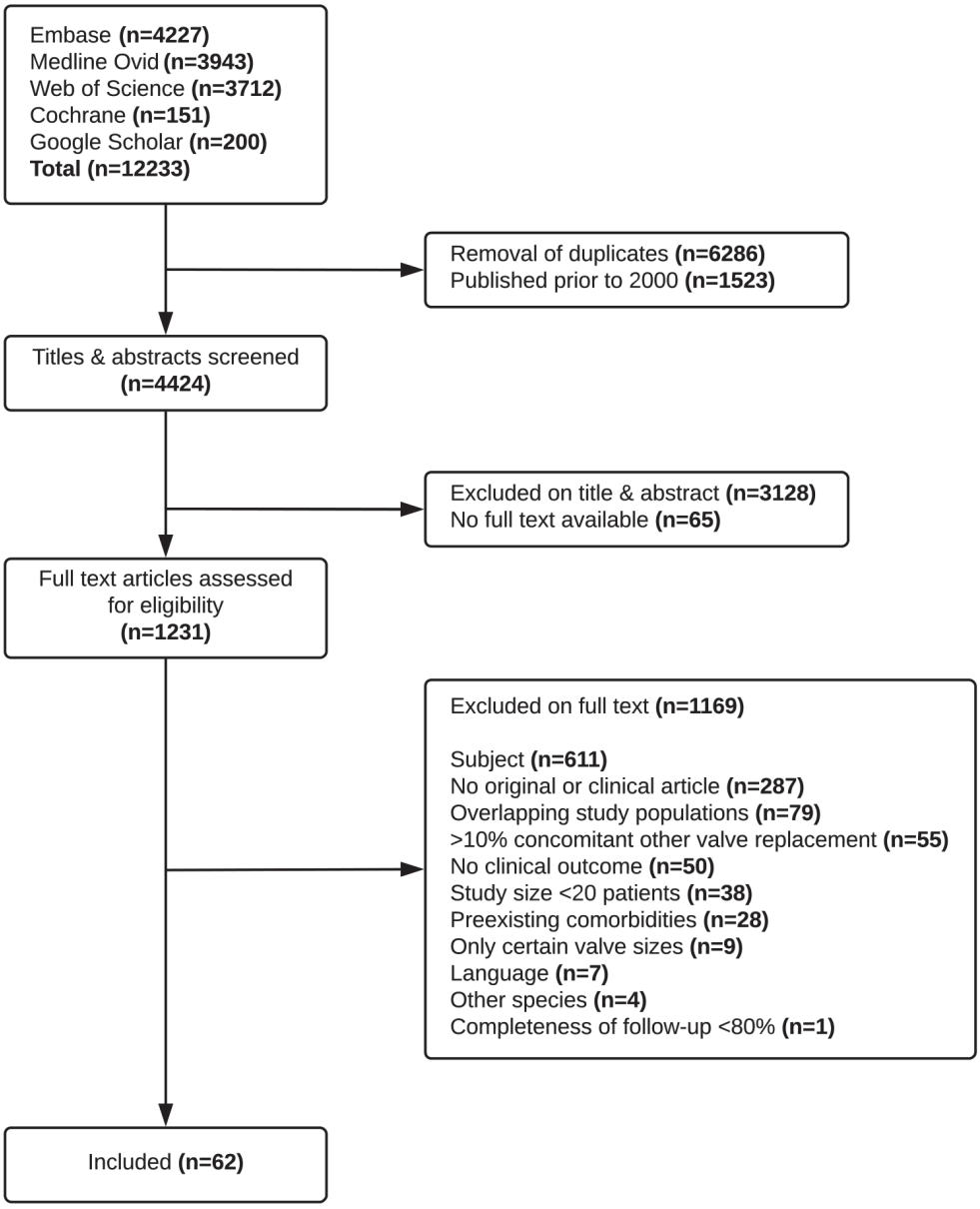


Figure S2. Flowchart of study selection.

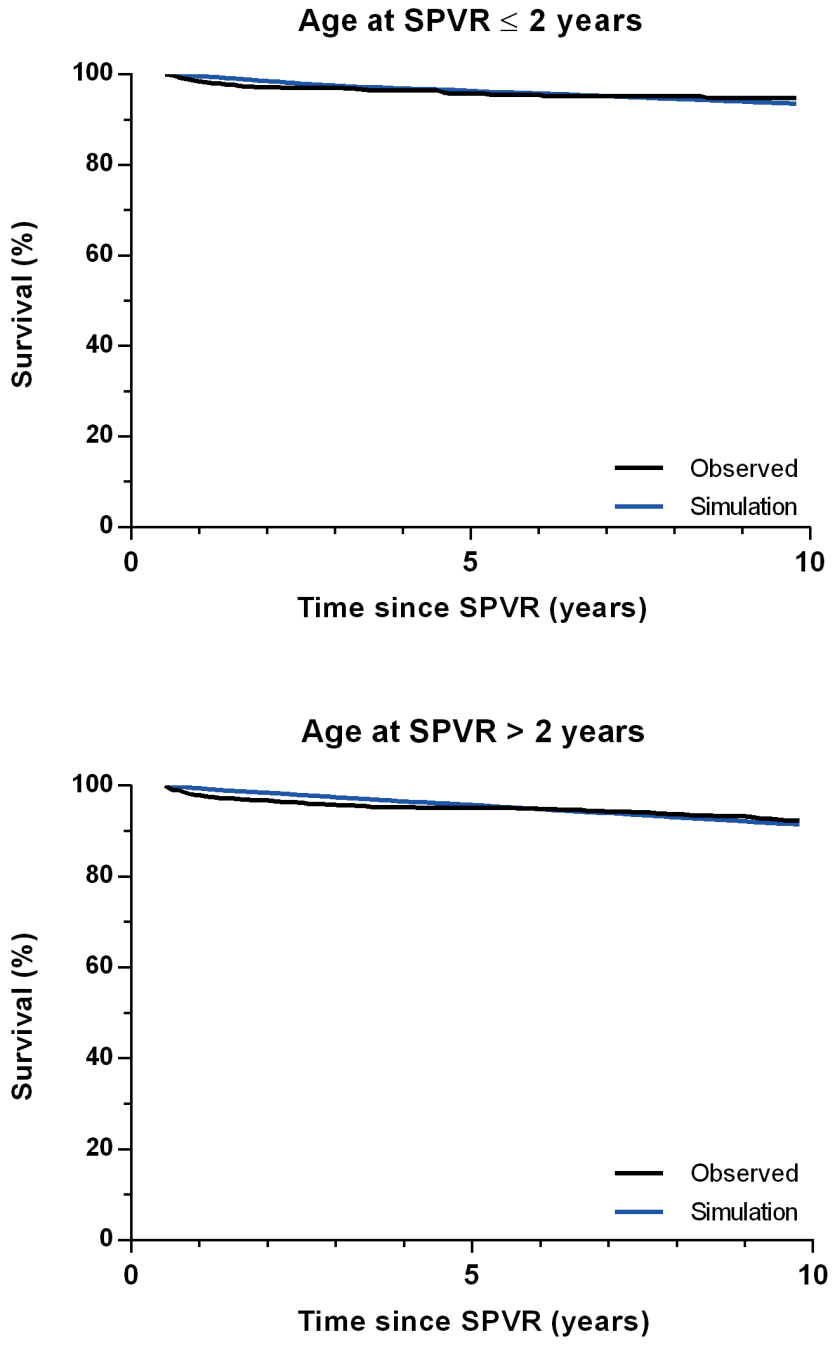


Figure S3. Internal validation of survival outcomes. Observed: pooled Kaplan-Meier survival curve.

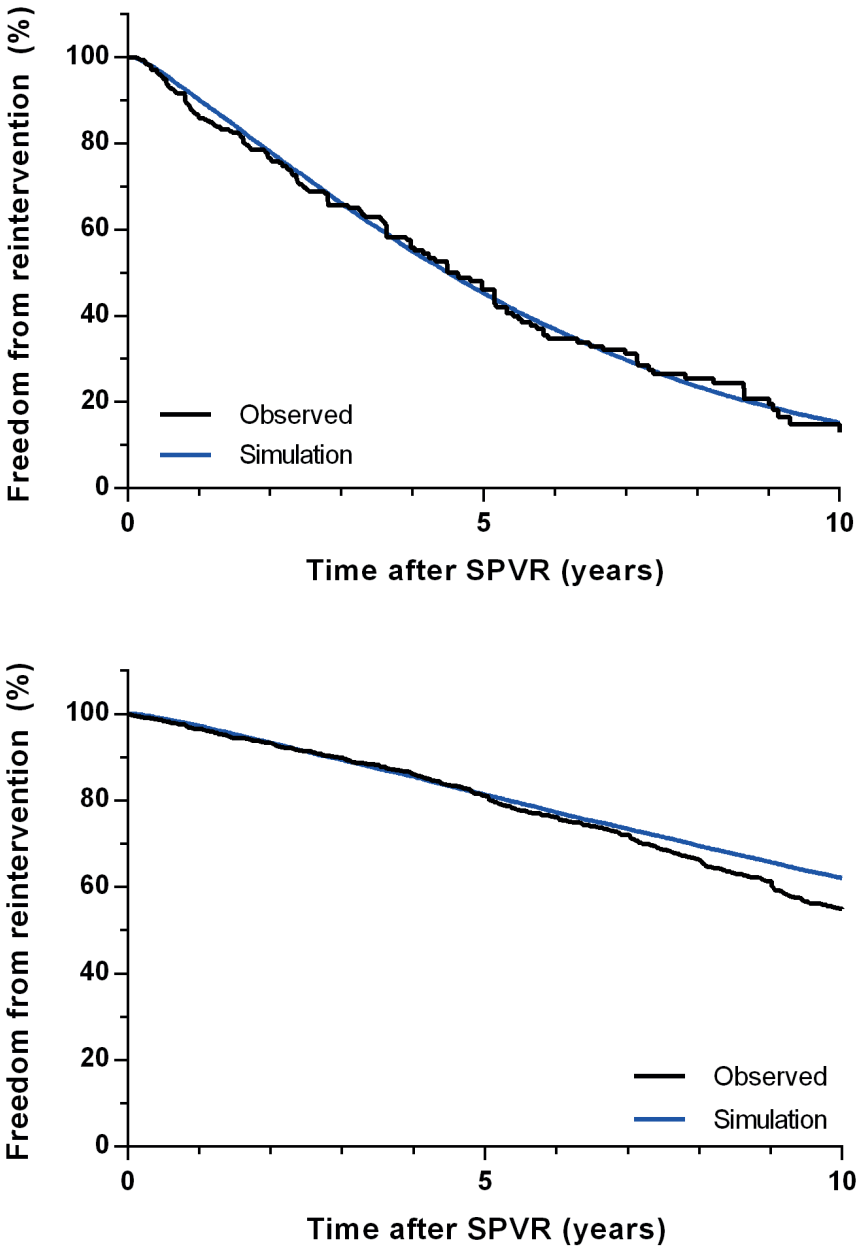
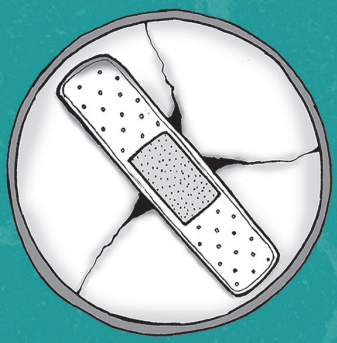


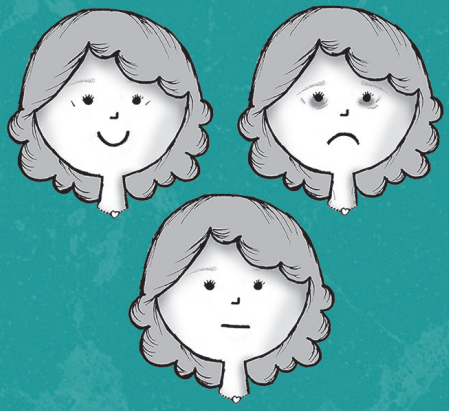
Figure S4. Internal validation of re-intervention outcomes. Observed: pooled Kaplan-Meier re-intervention curve.

References supplemental material

1. Liberati, A., et al., The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of internal medicine, 2009. 151(4): p. W-65-W-94.
2. Akins, C.W., et al., Guidelines for Reporting Mortality and Morbidity After Cardiac Valve Interventions. European Journal of Cardio-Thoracic Surgery, 2008. 33(4): p. 523-528.
3. Borenstein, M., et al., A basic introduction to fixed-effect and random-effects models for meta-analysis. Research Synthesis Methods, 2010. 1(2): p. 97-111.
4. Guyot, P., et al., Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol, 2012. 12: p. 9.
5. Centraal Bureau voor de Statistiek (CBS). Overlevingskansen; geslacht, leeftijd. 2016 3-8-2017 [cited 2017 18-1-2018]; Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70701ned/table?ts=1517913558300.
6. Knowles, R.L., et al., Patient-reported quality of life outcomes for children with serious congenital heart defects. Archives of disease in childhood, 2014: p. archdischild-2013-305130.
7. Heijink, R., et al., Decomposing cross-country differences in quality adjusted life expectancy: the impact of value sets. Population health metrics, 2011. 9(1): p. 1.
8. O'Hagan, A., M. Stevenson, and J. Madan, Monte Carlo probabilistic sensitivity analysis for patient level simulation models: efficient estimation of mean and variance using ANOVA. Health economics, 2007. 16(10): p. 1009-1023.
9. Zwaap, J.K., S; Meijden van der, C; Staal, P; Heiden van der, L, Kosteneffectiviteit in de praktijk, Z. Nederland, Editor. 2015.
10. Stolk, E.A., et al., Reconciliation of economic concerns and health policy. Pharmacoeconomics, 2004. 22(17): p. 1097-1107.
11. Versteegh, M.M., The iMTA Disease Burden Calculator. Software Version 1.3 beta. Downloaded from www.imta.nl/idbc. 2016, Institute of Medical Technology Assessment (iMTA), Erasmus University Rotterdam.
12. Zorginstituut, N., Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Diemen: Zorginstituut Nederland, 2015.
13. Lee, C., C.-H. Lee, and J.G. Kwak, Outcomes of redo pulmonary valve replacement for bioprosthetic pulmonary valve failure in 61 patients with congenital heart disease. European Journal of Cardio-Thoracic Surgery, 2016. 50(3): p. 470-475.
14. Poinot, N., et al., Pulmonary valve replacement after right ventricular outflow tract reconstruction with homograft vs Contegra®: a case control comparison of mortality and morbidity. Journal of cardiothoracic surgery, 2018. 13(1): p. 8.
15. Mohammadi, S., et al., Surgery for right ventricle to pulmonary artery conduit obstruction: Risk factors for further reoperation. Eur J Cardio-thorac Surg, 2005. 28(2): p. 217-222.
16. Latib, A., et al., Treatment and clinical outcomes of transcatheter heart valve thrombosis. Circulation: Cardiovascular Interventions, 2015. 8(4): p. e001779.

17. Huygens, S.A., et al., How much does a heart valve implantation cost and what are the health care costs afterwards? Open Heart, 2018. 5(1).
18. Geisler, B.P., et al., Cost-effectiveness and Projected Survival of Self-expanding Transcatheter versus Surgical Aortic Valve Replacement for High Risk Patients in a European Setting. A Dutch Analysis Based on the CoreValve High-Risk Trial. Structural Heart, 2017(just-accepted).
19. Andresen, B., et al., In-hospital cost comparison between percutaneous pulmonary valve implantation and surgery. European Journal of Cardio-Thoracic Surgery, 2016. 51(4): p. 747-753.
20. Özkan, M., et al., Ultraslow thrombolytic therapy: A novel strategy in the management of PROsthetic MEchanical valve Thrombosis and the prEdictors of outcomE: The Ultra-slow PROMETEE trial. American heart journal, 2015. 170(2): p. 409-418. e1.
21. Zorginstituut Nederland. Medicijnkosten. 2017 October 2, 2017]; Available from: http://www.medicijnkosten.nl/.
22. Kanters, T.A., et al., Update of the Dutch manual for costing studies in health care. PloS one, 2017. 12(11): p. e0187477.
23. Rothwell, P.M., et al., Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). The Lancet, 2004. 363(9425): p. 1925-1933.
24. Rivero-Arias, O., et al., Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. Medical decision making, 2010. 30(3): p. 341-354.
25. Cohen, D.J., et al., Evaluating the potential cost-effectiveness of stenting as a treatment for symptomatic single-vessel coronary disease. Use of a decision-analytic model. Circulation, 1994. 89(4): p. 1859-1874.
26. Amin, A.P., et al., Impact of bleeding on quality of life in patients on DAPT: insights from TRANSLATE-ACS. Journal of the American College of Cardiology, 2016. 67(1): p. 59-65.
27. Swedberg, K., et al., Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. The Lancet, 2010. 376(9744): p. 875-885.
28. van der Pol, S., et al., An Economic Evaluation of Sacubitril/Valsartan for Heart Failure Patients in the Netherlands. Value in Health, 2017. 20(3): p. 388-396.
29. Göhler, A., et al., Utility Estimates for Decision–Analytic Modeling in Chronic Heart Failure—Health States Based on New York Heart Association Classes and Number of Rehospitalizations. Value in Health, 2009. 12(1): p. 185-187.
30. Habib, G., et al., 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). European heart journal, 2015. 36(44): p. 3075-3128.





10

The risk in avoiding risk

Optimizing decision making in structural heart disease interventions

Mostafa M. Mokhles, Simone A. Huygens, Johanna J.M. Takkenberg.

Structural Heart. 2018;2(1):30-36

ABSTRACT

Due to public audit of operative mortality after cardiac surgery, surgeons tend to avoid procedures with high early mortality risk. However there may be considerable risks in avoiding this risk. Careful balancing of therapeutic options from both the clinical perspective, the patient perspective, and from societal perspective, including taking the long view on outcome, is essential for optimal tailoring of treatment to the individual patient in current clinical practice. Illustrated by three structural heart disease cases, all three perspectives are discussed in this paper. From a clinical perspective, the risk in avoiding risk may be minimized by developing and using novel prognostic models that are able to simultaneously combine several longitudinally collected data during patient follow-up with these patients' outcome. From a patient perspective, the implementation of patient information portals and decision aids, to support shared decision making, will empower and serve the individual patient in balancing risks and benefits. From an economic perspective, there might be a risk in avoiding risk by reimbursing interventions with a small decrease in risk associated with high costs, causing limited access to other healthcare interventions with higher health gains using the same amount of resources. Policy makers should therefore inform their funding decisions based on cost-effectiveness analyses. The tools described in this paper –reliable prognostic models for clinicians, decision aids for patients, and cost-effectiveness models for health care decision makers– will help to find an optimal balance in in 21st Century structural heart disease treatment decision making from all perspectives.

INTRODUCTION

In their 2011 BMJ paper Tom Treasure and colleagues asked the cardiovascular community the question "Is there a risk in avoiding risk?"[1] This question related to their observation that due to public audit of operative mortality after cardiac surgery, surgeons tend to avoid procedures with high early mortality risks. By focusing on early outcome, the long-term perspective for the patient may not always be optimally served. With their landmark paper they addressed a delicate issue in 21st Century cardiovascular interventional practice, namely the dire need for a broader view on balancing of risks and benefits of different treatment options. Careful balancing of therapeutic options from both the clinical perspective, the patient perspective, and from societal perspective, including taking the long view on outcome, is essential for optimal tailoring of treatment to the individual patient in current clinical practice. Illustrated by 3 structural heart disease cases, all 3 perspectives will be discussed in this paper.

DISCUSSION

Case 1: The clinical perspective: Balancing risks and timing of (re-)interventions

A 35 year old male patient presents with progressive fatigue and symptoms of palpitations. He was diagnosed with tetralogy of Fallot at birth and underwent primary repair at the age of 3 with the RVOT being reconstructed using a transannular pericardial patch. Current echocardiographic examination shows moderate pulmonary regurgitation.

The clinical challenge in this patient is to predict the optimal timing of reoperation and reconstruction of RVOT with, usually, an allograft. At this time there is no evidence-based consensus on optimal timing for RVOT reconstruction while the prevalence of adults with congenital heart disease increases at a rate of 5% per year. The risk in taking the risk of early surgery in patients with mild symptoms is that it can lead to more re-interventions during patient's life than strictly necessary. On the other hand the risk in avoiding risk by delaying surgery in such patients increases the risk of irreversible right ventricular (RV) dysfunction, RV failure and eventually death. It is important to take into account that most patients who need an RVOT reconstruction are young and therefore likely to require further surgery as prostheses have a limited lifespan. Carefully determining the optimal timing of surgery can significantly reduce the number of re-interventions in these patients during their lifetime while minimizing the risk of irreversible RV dysfunction. This example illustrates the need for reliable prognostic models that help clinicians to determine the optimal timing of (re-)intervention.

Although therapeutic and etiological research receives most attention in healthcare, prognostic research is evenly important when it comes to patient treatment. The aim of prognostic research is estimating the magnitude of risk in individual patients over a certain time period. This risk can include specific outcomes such as death, reoperation, stroke, but also outcome measurements such as quality of life impairment. Individual patient prognosis depends on patient (e.g. age, gender, comorbidities) and procedural characteristics. In order to be able to predict patient prognosis prognostic models are needed. These models can combine several patient and procedural characteristics to estimate the risk of a future outcome for the patients. Another important aspect of prognostic models is that they help to identify those patients that can benefit most from a particular treatment. Prognostic models can be used to estimate outcome on different levels: individual patient level, specific group of patients level and complete series level. Most current prognostic models perform reasonably well on the level complete series. However, their performance is far from optimal in the first two levels.

During the last decades at least 20 risk prediction models have been developed for patients in need of cardiac surgery, such as European System for Cardiac Operative Risk Evaluation (EuroSCORE 1 and 2) and the Society of Thoracic Surgeons (STS). However, none of these models is able to accurately predict the outcome of the individual patient after cardiac surgery.[2] From a clinical point of view, several reasons exist for the inadequate performance of currently available models. First of all, most models are developed using historical data and with continuous change in patient population over time these models can quickly become outdated. Furthermore, data used for the development of prognostic models is usually from a very heterogeneous patient population, making the model less accurate for certain subgroups of patients. In addition, the association between potential prognostic factors used for model building and patient outcome may also gradually change over time. From a statistical point of view, two important reasons exist for the inadequate performance of currently used prognostic models.

The first is that these models do not adequately correlate the *longitudinal data* that are collected during follow-up of patients (e.g. biomarkers, echocardiographic data, ECG's) with these patients' *clinical outcomes* (e.g. valve failure, reoperation, death). The second important reason for inadequate performance of current prognostic models is that they are all *static*, which means that once they are built they are no longer updated in the future while patient populations are continuously changing and new treatment options become available. All these shortcoming have a major influence on these models' discrimination and calibration capabilities. Furthermore, surgeons and other healthcare providers are usually interested in what the short-term result of the medical intervention is while the long-term outcome is of more importance for

individual patients. Therefore, ideally the starting point of scientific research should not be the procedure, but the individual patient and the end point the prospect of their future life. For example, there is no single 'best choice' in selecting a prosthetic valve for an individual patient since all these factors can be valued differently by individual patients. Patient may very well prefer a higher operation risk (e.g. Ross procedure vs mechanical valve) or a 60% life time risk of a reoperation with a bioprosthesis over a 20% life-time risk of a major TE or bleeding with a mechanical valve, or vice versa, depending on his or her preferences. This may result in taking a greater risk at short term if the consequence is a larger potential benefit for the patient on the long term (either survival and/or quality of life). In this regard, another major disadvantage of current prognostic models is that they put too much emphasis on early mortality and ignore other aspects of outcome such as long-term morbidity and mortality, and quality of life. It may cause decreased access to surgery/intervention for those who might benefit most. This *risk in avoiding risk* may be minimized by developing and using novel prognostic models that are able to simultaneously combine several longitudinally collected data during patient follow-up with these patients' outcome, as detailed below. These models do not only predict patient mortality but also patients quality of life and disease burden (e.g. number of reoperations).This approach is called joint-modeling and enable us to investigate, for example in our 35 year old patient, to what degree serial echocardiographic measurements (or certain biomarkers) are capable of predicting events (e.g. death or reoperation) that patients might experience after a certain treatment.[3-5]

The first step in creating a joint model is analyzing repeatedly collected data with longitudinal models. Several methods for longitudinal analyses exist. Both linear and non-linear structures can be used to analyze longitudinal data. In linear methods, the degree of the outcome (y) is determined by the degree of the input (x), which can be written as a y=ax+b equation. An important characteristic of linear methods is proportionality since there is a straight-line relationship between the input value and the outcome. Therefore, the behavior of linear methods can be fully predicted. In non-linear methods, the model uses parameters that are allowed to vary. Therefore, the assumption of proportionality is absent in non-linear models and the behavior of such model cannot be fully predicted. The cardiovascular system is a complex mechanical, chemical, and hemodynamic system in which the processes are often related via a variety of mechanisms. Therefore, these processes are often non-linearly structured. [6-8] Since the principle of proportionality may not be valid, using linear methods may result in simplification of the real process and, therefore, inaccurate results and inferences. On the other hand, the application of non-linear models is relatively time-consuming and requires advanced biostatistical expertise. The 2008 guidelines for reporting mortality and morbidity after cardiac valvular interventions propose the use

of longitudinal data analysis for series of assessments like repeated echocardiographic measurements of valve function to estimate it's average temporal pattern and variability in a group of patients.[9] These methods enables the researchers to model the trend of various repeatedly collected data such as echocardiographic measurements over time after allograft implantation. Using these methods it is possible to visualize the temporal trend of, for example, each aortic regurgitation grade over time during follow up. Clinicians can use such temporal trends to determine on average how for example aortic regurgitation develops over time after aortic allograft implantation. From a statistical perspective, these types of methods are superior and more informative compared to the methods where repeated outcomes are dichotomized and inadequately analyzed with actuarial methods as if they were events, such as freedom from grade 1+ or 3+ aortic regurgitation after aortic valve surgery.[10, 11] Assessing the trend of longitudinal outcomes of interest and identifying factors that influence these outcomes over time can be of particular importance since it can help the clinicians understand how a certain process changes over time and thus can contribute to a better patient management (e.g. by determining which patients should be monitored more closely by their physicians and at which time interval). The second step in creating a joint-model is combining the longitudinal analyses of repeated measurements with the events that patient may experience during follow-up. In joint-modeling, typically a mixed-effects model is used for the longitudinal data and a Cox model for the survival data in order to build a single model where dependency and association between these types of data is taken into account.[12] This approach can ultimately lead to a less biased and more efficient identification of potential prognostic factors of a certain outcome.[12] The joint-model can be constructed in way that it becomes dynamic which means that the prediction model will take into account time-dependent changes in patient population, risk factors, improvement in surgical techniques and improvements in the quality of pre-, peri- and postoperative patient care. The problem with the application of joint modeling is currently the complexity of the analyses and lack of appropriate software. It can be expected, however, that these issues will become less important when freely available and easy applicable software will become more readily available. This statistical method may significantly contribute to the optimal timing of a re-intervention for an individual patient with particular risk factors, such as our 35 year old patient with tetralogy of Fallot with pulmonary regurgitation.

Case 2: The patient perspective: Balancing risks, benefits and patient values

A 55 year old female presents with fatigue, and dyspnea on exertion. Echocardiographic examination reveals a bicuspid aortic valve, severe aortic regurgitation with normal annular and aortic root dimensions and a dilated LV.

The clinical challenge in this patient is in the appropriate selection of a surgical strategy to repair or replace the diseased valve, taking into account the risk and benefits of the different therapeutic options in relation to patient values and goals in life.

Therapeutic options for this patient include mechanical or bioprosthetic valve replacement, aortic valve repair, and some may argue the Ross operation. Since there are no perfect heart valve replacement options, as all surgical options carry substantial disadvantages, operated patients will either face the burden of mechanical valve implantation (anticoagulation-related and valve sound) or biological valve implantation/repair (limited durability). In addition the option of aortic valve repair and the Ross operation is restricted to a limited number of centers of excellence.

In particular younger adult prosthetic valve recipients face considerable lifetime risks of valve-related complications. Besides balancing the magnitude of these risks in selecting a heart valve prosthesis, there is also the need to balance patient values in relation to these risks. For example: one person may prefer a 100% lifetime risk of a reoperation on a biological valve over a 20% lifetime risk of a major bleeding with a mechanical valve, while others prefer the opposite, driven by their lifestyle, values and preferences. Also, in some circumstances a patient may be willing to trade in quantity of life for a better quality of life, or vice versa.

Aicher et al studied in a non-randomized setting quality of life and anxiety and depression after mechanical valve implantation, the Ross procedure and valve repair, and found that quality of life, including valve-related aspects such as bothersome valve sounds, frequency of medical visits, and fear of potential complications such as bleeding or reoperation for valve failure, is influenced by the type of operation.[13] Several other authors have reported comparable observations(INSERT REFS). It is therefore not surprising that there is increasing recognition of the necessity to address patient preferences in prosthetic heart valve selection, and both the ESC/EACTS and AHA/ACC VHD guidelines have implemented this in their recommendations (Class I, Level of Evidence C).[14, 15]

The concept of shared decision making is advocated on both sides of the Atlantic: patients should be fully informed about the indications for the surgery, risks of anticoagulant therapy and the potential need for and risk of reoperation in a shared decision-making process that accounts for the patient's values and preferences. Although both patients and clinicians find that shared decision making should be pursued we are far from optimal implementation of this concept.[16, 17] The use of patient decision aids to support the shared decision making process may be helpful in this regard. A recent randomized trial showed that although the use of a patient

decision aid to support prosthetic heart valve selection does not make valve selection less difficult, it did result in improved patient knowledge, and patients also felt better informed, less anxious and depressed, and experienced a better mental quality of life at the time of the decision making.[18] Interestingly, a randomized trial of a PCI choice decision aid for stable coronary artery disease that was published 2 months earlier, reported almost identical outcomes.[19] In addition, the same group studied cardiovascular clinicians' perceptions of shared decision making following use of the PCI choice decision aid and identified gaps in clinician knowledge around shared decision making, and reluctance among clinicians to modify their baseline practice, although they express their interest in using decision aids after they have been exposed to them in a research setting.[20] This suggests that the introduction of decision aids in cardiovascular clinical practice is not only effective in empowering patients, but may also help to instruct clinicians on optimal implementation of shared decision making in their clinical practice.[21]

From a patient perspective the future of clinical decision making in structural heart disease looks promising: with increasing emphasis on patient reported outcome measures and patient reported experience measures and the implementation of patient information portals and decision aids to support shared decision making, health care is slowly transforming to optimally empower and serve the individual patient in balancing risks and benefits, both short and long term. It does require a different role pattern: for doctors to take a more guiding role, and for patients to be proactive and become a full member of their own heart team.

Case 3: Societal perspective: Balancing risks, benefits and costs of treatment options

A 75 year old male with a history of COPD, diabetes mellitus type 2 and castration-resistant prostate cancer presents with severe symptomatic AS. Echo-Doppler evaluation reveals normalized cardiac chambers, septal and posterior wall thickness of 13 mm, normal left ventricular function, calcified aortic valve with a peak trans aortic flow velocity of 4.5 m/s. The clinical challenge in this patient is to select an appropriate strategy to treat his symptomatic AS, carefully weighing risks and benefits of the different treatment options, including informed patient preferences, while at the same time containing the costs of treatment given the short estimated life expectancy of this patient and the high costs associated with invasive treatment.

During the last decades, health expenditures have been rising across OECD countries. For instance in the US, the health expenditures per capita have increased from $327 in 1970, to $4,559 in 2000, and to $9,451 in 2015.[22] More importantly, not only absolute expenditure but also the relative share of the Gross Domestic Product (GDP) spent

on health has increased across OECD countries, for example in the US from 6.2% in 1970, to 12.5% in 2000, and to 16.9% in 2015.[22] This increase in health expenditures is expected to continue to rise in the coming decades, due to the ageing population but also due to technological developments.[23] Increasing health expenditures are also expected in the field of heart valve interventions. The ageing population in combination with the trend of increasing prevalence of valve disease with age will result in an increase in the number of patients requiring valve implantations.[24] Furthermore, there are many emerging technologies such as tissue-engineered heart valves and less invasive implantation methods.

As a consequence of these increasing healthcare expenditures, policymakers in all healthcare systems are faced with the challenge to keep their healthcare system financially viable in the long term while at the same time maintaining access to healthcare of good quality.[25] If resources are committed to one intervention, they are not available to fund and deliver other interventions.[25] Therefore policy makers should ask themselves whether an intervention is worth funding compared with other things they could do using the same resources.[26] The decisions of policy makers to fund one intervention carries the risk of inhibiting access to other interventions that might result in more health gains. The optimal situation from a societal perspective would be to allocate the limited resources in a way that maximizes the health of the overall population by avoiding the implementation of ineffective or comparatively inefficient interventions.[27] To achieve this, decisions about allocation of the limited resources should be informed by health technology assessment (HTA) studies. HTA is a multidisciplinary process where social, economic, organizational and ethical issues are evaluated, but the core of HTA is often the cost-effectiveness analysis.[28] Cost-effectiveness analysis seeks to identify which interventions offer health gains large enough, relative to their costs, to warrant reimbursement by the healthcare payer.[25] In a cost-effectiveness analysis two or more alternative interventions are compared in terms of their costs and health effects.[26] The main outcome of a cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER) which represents the average costs per quality adjusted life year (QALY) gained.[26] An intervention is cost-effective when the ICER is below a certain cost-effectiveness threshold, which is often set by policy makers. It is important to note that although cost-effectiveness analyses provide important information to policy makers, the efficacy, effectiveness, and availability (i.e. is the intervention reaching those who need it?) of the intervention should also be taken into account by policy makers.[26]

Considering cost-effectiveness in healthcare decision making influences the availability of transcatheter aortic valve implantation (TAVI) as a treatment option for the aforementioned patient. The cost-effectiveness of TAVI compared to currently used

interventions depends on whether the high costs of the TAVI device can be offset by cost reductions of other elements of the intervention, and if not, whether the higher costs of TAVI can be justified by increased survival and/or improved quality of life.[29]

Although the costs of TAVI are substantially higher than the costs of the alternative treatment for inoperable patients (often medical treatment), most cost-effectiveness studies have shown that this is compensated with a sufficient gain in QALYs resulting in acceptable cost-effectiveness estimates (i.e. ICER).[30, 31] In contrast, the cost-effectiveness of TAVI compared to SAVR in high-risk operable patients is less straightforward. The price of the TAVI device is substantially higher than the price of surgical valve prostheses (≈$30,000 or ≈€18,000 for TAVI devices versus ≈$5,000 or ≈€3,000 for surgical valve prostheses [29, 32]). The high TAVI device costs are partially compensated by a reduction in cost due to shorter procedure time and hospital stay, and lower use of blood products after TAVI compared to SAVR.[32-34] Despite these cost reductions, TAVI remains more expensive than SAVR.[31-34] The higher costs of TAVI compared to SAVR need to be compensated with benefits in health outcomes in order for TAVI to be cost-effective. Most cost-effectiveness studies have shown small differences in QALYs (ranging from -0.61[35] to 0.32[34] QALYs) after TAVI compared to SAVR, but the majority is in favour of TAVI.[31, 33, 34] These differences in estimated costs and health outcomes between studies have resulted in inconsistent cost-effectiveness estimates.[31, 33, 34] The large US trials and several model-based economic evaluations in other countries reported acceptable cost-effectiveness estimates[31, 33, 34], while other studies report less favourable cost-effectiveness estimates of TAVI compared to SAVR.[31] For more clarity on the cost-effectiveness of TAVI versus SAVR, additional cost-effectiveness analyses using data from real world clinical practice instead of randomized clinical trials are needed.

In addition to the use of TAVI in inoperable and high-risk operable patients, the use of TAVI in intermediate-risk operable patients has been studied. Recently, two large randomized clinical trials have shown that TAVI is non-inferior to SAVR in intermediate-risk patients regarding mortality and disabling strokes.[36, 37] Since there is no survival benefit, the costs of TAVI need to be lower and/or the quality of life after TAVI needs to be higher than after SAVR in order for TAVI to be cost-effective compared to SAVR in these patients. However, the reduction in costs due to the shorter length of hospital stay of approximately three days seems too small to offset the high TAVI device costs[36] and the quality of life difference in patients after TAVI compared to SAVR in intermediate-risk patients is unknown. Therefore cost-effectiveness studies estimating the exact cost difference and the survival and/or quality of life benefits are necessary to determine the cost-effectiveness of TAVI compared to SAVR in intermediate-risk patients.[29]

But how can these cost-effectiveness estimates implicate the access to TAVI for patients? As mentioned before, policy makers can use these estimates when deciding about spending the healthcare resources to fund TAVI. In other words, the policy makers decide whether or not the costs of TAVI will be reimbursed by the healthcare payer. The use of an intervention is heavily dependent on this reimbursement.[38] The cost-effectiveness estimates of TAVI compared to standard treatment have resulted in the reimbursement and therefore adoption of TAVI as a treatment for inoperable patients in many countries. In contrast, there is a lot of variation in the reimbursement of TAVI in high-risk operable patients.[38] For example, TAVI is fully reimbursed in Germany, while the reimbursement of TAVI for operable patients in the UK is still under review because the evidence on the efficacy of TAVI has been found inadequate.[39] This has profound implications for the adoption of TAVI: in countries where TAVI is fully reimbursed, the number of TAVIs performed was substantially higher than in countries with constrained reimbursement of TAVI.[38] Although there may be more reasons for the lower adoption of TAVI in some countries, the questionable cost-effectiveness of TAVI versus SAVR could have influenced the policy makers' decision for constrained reimbursement of TAVI in some countries resulting in limited access to TAVI.

From an individual patient perspective, the limited access to TAVI might seem unfair, as patients might want to benefit from the minimal invasive nature of TAVI compared to SAVR. However, considering the health of the overall population, this choice can be justified since the resources that would have been spend on TAVI if policy makers had decided to fully reimburse its costs, now can be spend on other interventions that deliver more health gains using the same resources. However, this might change in the future because it is expected that, as TAVI is being performed more frequently, market forces will decrease the price of the TAVI device.[32, 40] If this results in a cost reduction of the TAVI procedure that results in undoubtful cost-effectiveness of TAVI versus SAVR, then the risk of foregoing health benefits due to not being able to spent the resources on other healthcare is compensated by the value for money provided by TAVI.

From an economic perspective, the answer to the question "Is there a risk in avoiding risk?" is that there might be a risk of avoiding risk by reimbursing an intervention with a small decrease in risk associated with high costs (i.e. high ICER). This risk would entail limited access to other healthcare interventions that might have provided more health gains using the same amount of resources. To avoid this risk, policy makers should inform their funding decisions with results from cost-effectiveness analyses. Ideally, this would lead to an allocation of the limited available resources that maximizes the health of the overall population.

Conclusion

From all possible perspectives –clinical, patient and society- there may be a risk in avoiding risk in 21st Century structural heart disease treatment decision making. The tools described in this paper –reliable prognostic models for clinicians, decision aids for patients, and cost-effectiveness models for health care decision makers– will help to find an optimal balance in decision making from all perspectives. By taking this diversity of perspectives into account, including the short and long term perspective on outcomes, we are entering a new exciting era that moves away from 'risk' management (and short sighted risk avoidance) toward 'value-driven' management of structural heart disease.

Funding. Simone Huygens is funded by the Netherlands Cardio Vascular Research Initiative: The Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences (1Valve consortium). Mostafa Mokhles is funded by the Netherlands Organisation for Scientific Research (VENI grant).

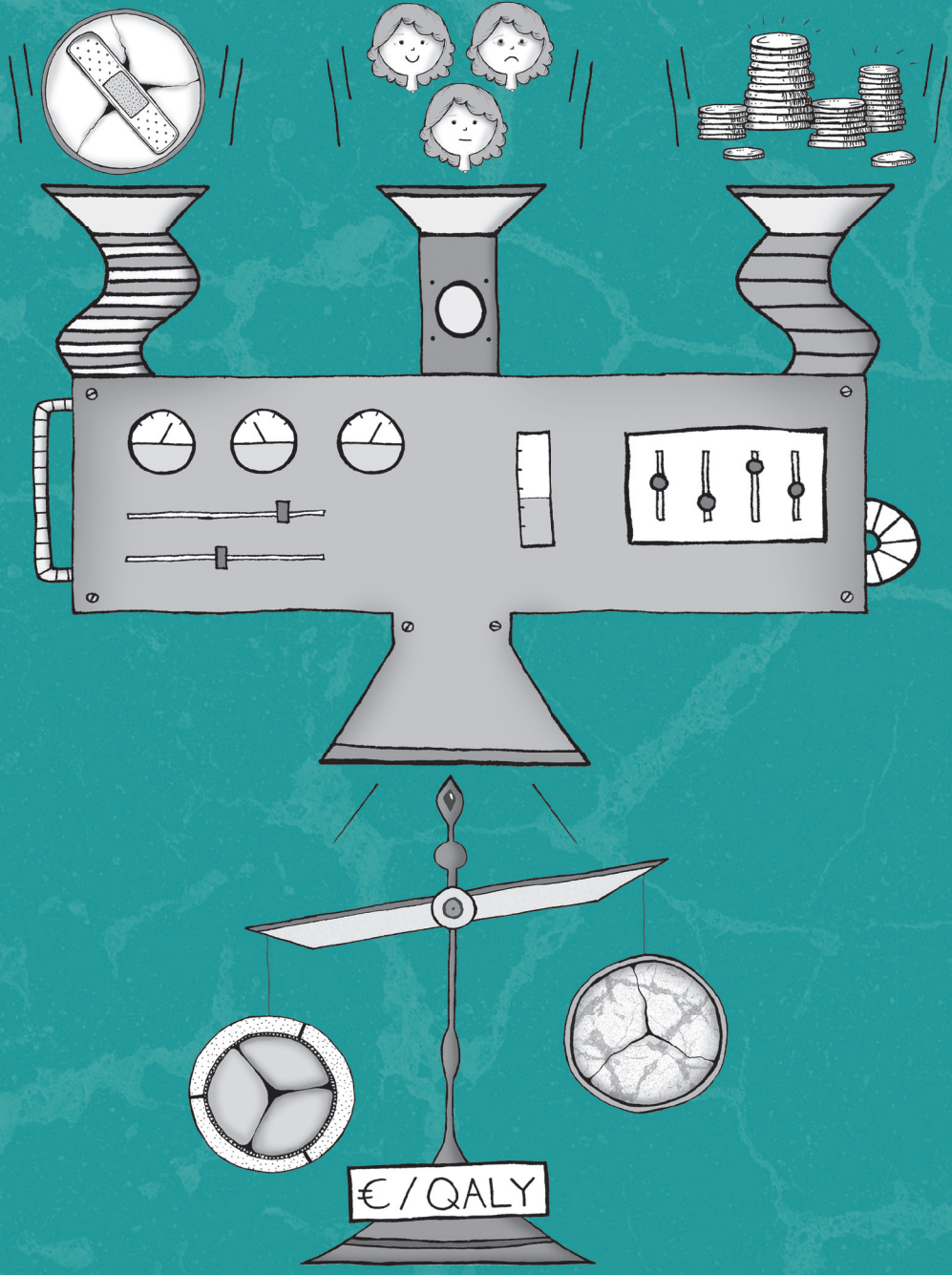
Conflicts of interest. None.

REFERENCES

1. Treasure, T., A. Hasan, and M. Yacoub, Is there a risk in avoiding risk for younger patients with aortic valve disease. BMJ, 2011. 342: p. d2466.
2. Prins, C., et al., Cardiac surgery risk-stratification models. Cardiovasc J Afr, 2012. 23(3): p. 160-4.
3. Andrinopoulou, E.R., et al., An introduction to mixed models and joint modeling: analysis of valve function over time. Ann Thorac Surg, 2012. 93(6): p. 1765-72.
4. Henderson, R., P. Diggle, and A. Dobson, Joint modelling of longitudinal measurements and event time data. Biostatistics, 2000. 1(4): p. 465-80.
5. Wulfsohn, M.S. and A.A. Tsiatis, A joint model for survival and longitudinal data measured with error. Biometrics, 1997. 53(1): p. 330-9.
6. Elbert, T., et al., Chaos and physiology: deterministic chaos in excitable cell assemblies. Physiol Rev, 1994. 74(1): p. 1-47.
7. Sugihara, G., et al., Nonlinear control of heart rate variability in human infants. Proc Natl Acad Sci U S A, 1996. 93(6): p. 2608-13.
8. Scher, A.M. and A.C. Young, Nonlinearity in the control of blood pressure and heart rate. Ann N Y Acad Sci, 1969. 156(2): p. 722-30.
9. Akins, C.W., et al., Guidelines for reporting mortality and morbidity after cardiac valve interventions. J Thorac Cardiovasc Surg, 2008. 135(4): p. 732-8.
10. Murashita, T., et al., Long-term results of aortic valve regurgitation after repair of ruptured sinus of valsalva aneurysm. Ann Thorac Surg, 2002. 73(5): p. 1466-71.
11. Losay, J., et al., Aortic valve regurgitation after arterial switch operation for transposition of the great arteries: incidence, risk factors, and outcome. J Am Coll Cardiol, 2006. 47(10): p. 2057-62.
12. Ibrahim, J.G., H. Chu, and L.M. Chen, Basic concepts and methods for joint models of longitudinal and survival data. J Clin Oncol, 2010. 28(16): p. 2796-801.
13. Aicher, D., et al., Quality of life after aortic valve surgery: replacement versus reconstruction. J Thorac Cardiovasc Surg, 2011. 142(2): p. e19-24.
14. Nishimura, R.A., et al., 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, 2014. 129(23): p. e521-643.
15. Joint Task Force on the Management of Valvular Heart Disease of the European Society of, C., et al., Guidelines on the management of valvular heart disease (version 2012). Eur Heart J, 2012. 33(19): p. 2451-96.
16. Korteland, N.M., et al., Prosthetic aortic valve selection: current patient experience, preferences and knowledge. Open Heart, 2015. 2(1): p. e000237.
17. Korteland, N.M., et al., Cardiologist and cardiac surgeon view on decision-making in prosthetic aortic valve selection: does profession matter? Neth Heart J, 2014. 22(7-8): p. 336-43.
18. Korteland, N.M., et al., Does the Use of a Decision Aid Improve Decision Making in Prosthetic Heart Valve Selection? A Multicenter Randomized Trial. Circ Cardiovasc Qual Outcomes, 2017. 10(2).

19. Coylewright, M., et al., PCI Choice Decision Aid for Stable Coronary Artery Disease: A Randomized Trial. Circ Cardiovasc Qual Outcomes, 2016. 9(6): p. 767-776.
20. Coylewright, M., et al., PCI Choice: Cardiovascular clinicians' perceptions of shared decision making in stable coronary artery disease. Patient Educ Couns, 2017. 100(6): p. 1136-1143.
21. Treasure, T., et al., Developing a shared decision support framework for aortic root surgery in Marfan syndrome. Heart, 2017: p. heartjnl-2017-311598.
22. OECD. Health spending (indicator). 2017 [cited 2017 31 March]; Available from: https://data.oecd.org/healthres/health-spending.htm.
23. de Meijer, C., et al., The effect of population aging on health expenditure growth: a critical review. European Journal of Ageing, 2013. 10(4): p. 353-361.
24. Nkomo, V.T., et al., Burden of valvular heart diseases: a population-based study. The Lancet, 2006. 368(9540): p. 1005-1011.
25. Woods, B., et al., Country-level cost-effectiveness thresholds: initial estimates and the need for further research. Value in Health, 2016. 19(8): p. 929-935.
26. Drummond, M.F., et al., Methods for the economic evaluation of health care programmes. 2015: Oxford university press.
27. Siebert, U., When should decision-analytic modeling be used in the economic evaluation of health care? Eur J Health Econom, 2003. 3: p. 143.
28. World Health Organization. Health Technology Assessment. 2017 [cited 2017 5 April]; Available from: http://www.who.int/medical_devices/assessment/en/.
29. Reynolds, M.R., S.J. Baron, and D.J. Cohen, Economic Implications of Transcatheter Aortic Valve Replacement in Patients at Intermediate Surgical Risk. Circulation, 2016. 134(19): p. 1416-1418.
30. Reynolds, M.R., et al., Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). Circulation, 2012. 125(9): p. 1102-1109.
31. Huygens, S.A., J.J.M. Takkenberg, and M.P.M.H. Rutten-van Mölken, Systematic review of model-based economic evaluations of heart valve implantations. The European Journal of Health Economics, 2017: p. 1-15.
32. Osnabrugge, R.L.J., et al., Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. The Annals of thoracic surgery, 2012. 94(6): p. 1954-1960.
33. Reynolds, M.R., et al., Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A). Journal of the American College of Cardiology, 2012. 60(25): p. 2683-2692.
34. Reynolds, M.R., et al., Cost-effectiveness of transcatheter aortic valve replacement with a self-expanding prosthesis versus surgical aortic valve replacement. Journal of the American College of Cardiology, 2016. 67(1): p. 29-38.
35. Orlando, R., et al., Cost-effectiveness of transcatheter aortic valve implantation (TAVI) for aortic stenosis in patients who are high risk or contraindicated for surgery: A model-based economic evaluation. Health Technol Assess, 2013. 17(33): p. 1-86.

36. Leon, M.B., et al., Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med, 2016. 2016(374): p. 1609-1620.
37. Reardon, M.J., et al., Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. New England Journal of Medicine, 2017.
38. Mylotte, D., et al., Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. Journal of the American College of Cardiology, 2013. 62(3): p. 210-219.
39. National Institute for Health and Care Excellence, Transcatheter aortic valve implantation for aortic stenosis. NICE interventional procedure guidance [IPG421]. 2012, NICE.
40. Brown, A., B.J. Meenan, and T.P. Young, Marketing innovation: medical device prices follow the experience curve. Journal of Medical Marketing, 2007. 7(3): p. 203-212.


€ / QALY

11

General discussion

Currently available heart valve substitutes are all associated with considerable disadvantages. Patients with biological valves face the prospect of re-intervention due to limited durability of these heart valve substitutes, while recipients of mechanical valves need lifelong anticoagulation treatment which is associated with increased bleeding risk and complications during pregnancy. But there may be a bright future ahead as tissue-engineering provides a promising method to create living heart valves with growth potential that can last a lifetime without the need of lifelong anticoagulation treatment. In this thesis, early Health Technology Assessment (HTA) of tissue-engineered heart valves (TEHV) was performed to assess the potential of TEHV to improve health outcomes and reduce costs. In this chapter, the three lines of research in this thesis are discussed: (1) model development, (2) health outcomes and costs of existing heart valve substitutes, and (3) early HTA of TEHV in the aortic position in elderly and pulmonary position in children. Further, the implications for different stakeholders are addressed, conclusions are drawn and recommendations for further research are given.

1. MODEL DEVELOPMENT

To be able to estimate health outcomes and costs after heart valve replacements with current and future heart valve substitutes we needed a decision-analytic model. The development of the conceptual model that served as the foundation for our decision-analytic model started with a systematic review of model-based economic evaluations of heart valve implantations published in the literature ***(Chapter 2)***. The shortcomings identified in the methodological quality assessment performed in this review were avoided in this thesis by being transparent about model development, providing detailed descriptions of sources of input parameters and modelling methods, and using direct utility assessment with a preference-based quality of life instrument instead of indirect utility assessment using New York Heart Association (NYHA) class. Subsequently, a draft conceptual model was discussed with a Delphi panel of ten experts, including cardiothoracic surgeons, cardiologists, and a biomedical scientist. This resulted in a conceptual model reflecting the most important consequences after heart valve interventions based on the views of a multidisciplinary group of experts ***(Chapter 3)***.

The Delphi technique is designed as a group communication process which aims to achieve a convergence of opinion on a specific issue.[38] After one round of individual discussions and two rounds of surveys, the Delphi panel reached consensus on most issues regarding the conceptual model, but there were some events for which consensus could not be reached. First, the inclusion of TIA's in addition to strokes as

cerebrovascular accidents (CVA) was questioned by some experts. Initially, we decided to include TIA's, however this appeared to be not feasible because in the data source (Adult Cardiac Surgery Database, ACSD) used for the occurrence of strokes in the first 30 days after surgical aortic valve replacement (SAVR), the definition of CVA was limited to strokes. However, the in- or exclusion of TIA's would not have influenced the cost-effectiveness results because we assumed that TEHV would not reduce the risk of strokes in elderly patients after SAVR or transcatheter aortic valve implantation (TAVI) with bioprostheses and strokes were not reported to occur in children after right ventricular outflow reconstruction (RVOTR) ***(Chapter 9)***. Second, there was discussion about including or excluding atrial fibrillation during the first 30 days or not. Eventually, we included all arrhythmias after SAVR to be in line with the definition used in the ACSD. However, since we assumed early event risks to be comparable for TEHV and existing heart valve substitutes, in- or exclusion of this event did not have a large influence on the cost-effectiveness results. Finally, there was discussion about including myocardial infarction and pacemaker implantation only during the first 30 days or during the patient's entire lifetime. We intended to perform sensitivity analysis on this issue by including these events during both time periods, however this was not feasible due to limited reports on these long-term events.

During the execution of the early HTA of TEHV, it became apparent that we had to make some changes in the conceptual model. First, in addition to strokes and atrial fibrillation, we had to change the definitions of acute kidney injury to renal failure for SAVR patients to be in line with the definition used in the ACSD. Second, conversion to another approach (transcatheter to surgical valve implantation and vice versa) was included as an event in the conceptual model, but was not included in the final decision analytic model. Emergent conversion from TAVI to SAVR occurs rarely (1.2%-2.1%) and according to expert opinion conversion from SAVR to TAVI occurs even less.[39, 40] In addition, since the causes of conversion are not related to the prosthetic heart valve itself, the conversion rate is likely to be comparable for TEHV and existing heart valve substitutes.[40] Therefore, we did not include conversion to another approach in our final model.

To our knowledge, this thesis describes the first patient-level simulation model (also called a microsimulation model) to estimate the cost-effectiveness of heart valve implantations. We chose a patient-level simulation model over a decision tree or cohort state transition model (also known as Markov model) because it has the ability to incorporate recurrence of events and to "remember patient history" without leading to an unmanageable number of health states.[41, 42] There are mainly two types of patient-level simulation models: discrete event simulation (DES) and individual-level state transition models. We chose a DES model because

in these models time-to-event is described stochastically rather than with fixed time intervals, which allows the optimal use of data describing the time to each event.[42] This is also possible in individual-level state transition models by using very short cycle lengths, but this might lead to increased computer time.[42] We strived to use the memory of our patient-level simulation model to make survival, valve-related events, utilities, and costs dependent on patient and intervention characteristics and patient history (i.e. previous events). However, in contrast to costs ***(Chapter 8 and 9)***, early clinical outcomes, and utilities (in ***Chapter 8***), long-term clinical outcomes in the early HTA studies were not dependent on patient and intervention characteristics or patient history. The reason that we could not incorporate this in our model was the limited data availability on long-term clinical outcomes. As a result, we could not model patient-specific risks on valve-related events or mortality, except for early outcomes after aortic valve replacement, and we could not adjust risks on subsequent events or mortality after events. Similarly, there was a lack of data on utilities in children.

2. HEALTH OUTCOMES AND COSTS OF EXISTING HEART VALVE SUBSTITUTES

Before we could perform cost-effectiveness analyses with our decision-analytic model, data needed to be collected on the input parameters of the model. Since TEHV are not implemented in clinical practice yet, assumptions had to be made about their performance and costs. On the other hand, the performance and costs of existing heart valve substitutes could be based on evidence from clinical practice.

2.1 Clinical input parameters

The clinical input parameters can be divided in early (within 30 days after the intervention) and late (beyond 30 days after the intervention) mortality and valve-related events risks and rates. Early mortality risk after aortic valve implantation in elderly patients was 4% after SAVR and 5% after TAVI ***(Chapter 8)***. In the past decades, improvements in diagnosis and perioperative management have resulted in decreased early mortality risk after SAVR ***(Chapter 4)***. The most common early events after SAVR and TAVI differ; vascular complications, bleeding, and pacemaker implantation occur more often after TAVI, while arrhythmias have a higher occurrence after SAVR ***(Chapter 8)***. Thromboembolism was the most frequently occurring late valve-related event after SAVR and TAVI. However, the thromboembolism rate was close to the occurrence rate in the age and sex matched general population[43], which suggests that factors other than heart valve disease (such as increasing incidence of atherosclerotic disease with age) may have a larger influence on the risk of thromboembolism in elderly patients.

[44] Although there is a high probability that elderly patients will not outlive the durability of the implanted aortic bioprosthesis, the lifetime risk of re-intervention was not absent (9% in 75-year olds; ***Chapter 5***). Therefore there are still potential benefits to be gained in this patient population with a heart valve substitute that is less prone to degeneration than bioprostheses.

In the early HTA of TEHV in the aortic position in elderly patients, both SAVR and TAVI are included as comparator treatments ***(Chapter 8)***. Several findings in this thesis suggest that relatively healthy elderly patients are selected for SAVR. First, the similarity between the survival after SAVR with bioprostheses and the survival in the age and sex matched general population suggests the careful selection of relatively healthy elderly patients to undergo SAVR. This finding is supported by the cost analysis in ***Chapter 7*** where we found lower healthcare costs of nursing homes in elderly patients after SAVR compared to the general population.[45] In addition, not only the use of formal elderly care, but also informal care use was lower in elderly SAVR patients than in the general population ***(Chapter 6)***. These findings suggest that the proportion of patients with treated aortic valve disease who can still live independently is higher than in the general elderly population. Patients that are rejected for SAVR due to comorbidities and/or frailty are referred to medical treatment or TAVI. Therefore, it is not surprising that the background mortality in TAVI patients was 50% higher than in the general population ***(Chapter 8)***.

Due to the relatively low prevalence of congenital heart disease affecting the pulmonary valve, the reports on outcome after RVOTR are predominantly based on small single-center studies. Furthermore, these series often represent patients with a widespread variety of rare congenital heart defects and the long-term follow-up is limited. In ***Chapter 9***, the available evidence on outcomes after RVOTR was summarized in a systematic review and meta-analysis. The early mortality was considerably higher in children below the age of two years (11%) than in older children undergoing RVOTR (5%). The five-year freedom from re-intervention in these patients is low (46.1% in patients aged ≤2 years and 81.1% in patients aged >2 years at RVOTR) because the patients outgrow the heart valve substitute when they get older. This underlines the importance of developing a living heart valve substitute that can accommodate patient growth and reduces this need for re-intervention.

Clinical input parameters of existing heart valve substitutes were based on real world clinical data, mostly derived from patient registries or systematic reviews and meta-analyses of observational studies ***(Chapter 4, 5 and 9)***. Strengths of using input parameters derived from the meta-analyses described in this thesis are that input parameters are based on real world data from clinical centres around the world, all

available evidence is systematically reviewed and included in the meta-analysis if the inclusion criteria are fulfilled, and the sample size is increased and therefore provides more power to identify small effects sizes.[46, 47] However, meta-analyses are also associated with limitations. The methodological quality or reporting of the original studies cannot be improved.[46, 47] For example, it is possible that selection bias of patients included in observational studies influenced the outcomes. Furthermore, there may be publication bias, as significant results ar more likely to get published, while negative or insignificant results may not be submitted or accepted for publication.[46, 47]

The availability of long-term patient-level time-to-event data of survival and valve-related events after heart valve implantations was limited. This means that although our decision-analytic model has the flexibility to model time to events stochastically, this could not be implemented for most of the long-term valve-related events. Fortunately, we were able to include a time-varying hazard for structural valve deterioration of biological valves accounting for the accelerated hazard over time due to degeneration of the prosthetic heart valve. This time-varying hazard was based on individual patient data extracted from published Kaplan-Meier curves ***(Chapter 5 and 8)***.[48, 49] However, the limited data available on the time of prosthetic valve endocarditis prevented us to include the time-varying hazard of this event described by Blackstone et al., namely an early peaking phase with the highest hazard at six months that merges in to a constant phase of low risk after about twelve months.[48, 49] Instead we had to assume a constant hazard for prosthetic valve related endocarditis and the other valve-related events using pooled linearized occurrence rates derived from meta-analyses.

The Dutch HTA guidelines prescribe the use of a time horizon that is long enough to capture all differences in costs and effects of the compared interventions, preferably a lifetime horizon.[34] The effects of TEHV are expected to have large impacts during the entire life of the patient. Unfortunately, the limited data on long-term outcomes after heart valve interventions prevented us from applying this lifetime horizon in the early HTA of TEHV in the pulmonary position in children ***(Chapter 9)***. Although we could have extrapolated the results of the meta-analysis on outcomes after pulmonary valve replacement in children for the rest of their lives, we decided not to because this would introduce substantial uncertainty in our outcomes that we could not model. In contrast, we did apply this extrapolation in the early HTA of TEHV in the aortic position in elderly ***(Chapter 8)***. However, the relatively short remaining life expectancy in these patients allowed us to apply a lifetime horizon without introducing too much uncertainty.

One of the ways to enhance confidence in the model's results is to examine the external validity.[50] External validation compares a model's results to actual event data from

a source other than the one that was used to estimate the input parameters.[50] In ***Chapter 8*** external validation was conducted comparing survival and time-to-events after SAVR as derived from of our model (applying US survival tables for background mortality) with an external dataset from the US Providence Health System in Portland. [50] The survival outcomes derived from the model and observed in the Portland dataset were comparable, but the model predicted a slightly higher survival, while the occurrence of valve-related events was higher in the model compared to the Portland dataset. The differences may be explained by limited representativeness of the US patients and healthcare compared to the Netherlands, underreporting of events, too short-follow-up in the Portland dataset, or differences in outcomes between the US and the Netherlands. Unfortunately, it was not possible to investigate the external validation of the outcomes after TAVI or RVOTR because we did not have access to an external dataset in these patient populations.

2.2 Utilities

Utilities after aortic valve implantations were based on patient-reported health-related quality of life measured with the EQ-5D-5L ***(Chapter 6)***. In addition to SAVR and TAVI patients, ***Chapter 6*** also includes adult RVOTR patients. On average, SAVR and TAVI patients had a lower utility than the general population, while RVOTR patients had a slightly higher utility than the general population. The results in ***Chapter 6*** suggest that this is mainly due to better mental health, since physical health was considerably poorer in RVOTR patients than in the general population. This is in line with previous research that showed that patients after RVOTR or with congenital heart disease in general have better mental health, more satisfaction with life, and better emotional functioning than the general population.[51-53] Opić et al. suggested that this might be explained by overcompensation, social desirability or response shift.[51] Response shift is the phenomenon that patients have different internal standards and values after a life-threatening experience, such as cardiac surgery. In other words, they may worry less about futilities in life.[51] The reason we did not observe this effect in SAVR and TAVI patients may be that they are not as used to living with health problems because aortic valve disease is often acquired later in live, and therefore they may have a different perspective on their current health status than patients with congenital heart disease.

The RVOTR patients included in ***Chapter 6*** were all adults. Unfortunately, we were not able to collect EQ-5D utilities in children for the application in the early HTA of TEHV in the pulmonary position ***(Chapter 9)***. The reason for this was two-fold, on the one hand, the annual number of children who undergo RVOTR is low making it unfeasible to collect data on a large number of patients in a short time period, on the other hand, there are no health state values available for the EQ-5D-Y (i.e. the EQ-5D version

for children and adolescents) to translate health-related quality of life outcomes to utilities. Instead the baseline utility in ***Chapter 9*** of children after RVOTR was estimated by applying the relative difference of health-related quality of life measured with the Pediatric Quality of Life Inventory (PedsQL) of children with serious congenital heart defects in the United Kingdom to the EQ-5D utility of young adults in the Dutch general population.[54, 55] In this approach, we might have unrightfully assumed that the scales of the PedsQL and EQ-5D are comparable. Furthermore, by adapting EQ-5D utilities of adults, we assumed that the health state valuation of the general population is not dependent on age, although there is evidence that suggests that respondents' age has (a relatively small) impact on the health state values.[56] However, despite these shortcomings, it is not expected that any inaccuracies in the estimated baseline utility of RVOTR patients had a large impact on the cost-effectiveness results reported in ***Chapter 9*** because the baseline utility was equal for the intervention and comparator arm. Moreover, a recent Dutch health state valuation study of the EQ-5D-Y found comparable health state values for children and adults.[57] This suggests that the Dutch general population does not value health states in children differently from the same health states in adults, which may justify our adaptation of EQ-5D utilities of adults to children. However, these results are specific to the Netherlands and may not be generalisible to other countries.

2.3 Costs

Economic evaluations can be performed from a healthcare or societal perspective, depending on which costs and effects are included. About half of the national HTA guidelines, including those of the Netherlands, prescribe a societal perspective.[34, 58] This means that all relevant costs and effects should be included, regardless of who bears the costs and who receives the benefits. Costs can be divided into costs inside and outside the healthcare system.

Costs inside the healthcare system include healthcare costs directly related to the intervention or events and costs of healthcare utilisation in life years gained. In line with the new Dutch HTA guidelines introduced in 2015 both types of healthcare costs were included in our early HTAs.[34] Healthcare costs were based on retrospective analyses of Dutch health insurance claims data of patients who had undergone heart valve implantations in 2010-2013 ***(Chapter 7)***. The use of Dutch health insurance claims data gave us the opportunity to include healthcare costs of practically all patients who underwent a heart valve implantation in the Netherlands, because 99% of all Dutch residents are insured. Moreover, we not only had access to healthcare costs related to the heart valve intervention, but also all other healthcare costs. The impact of including these costs on the cost-effectiveness ratio was shown by Van Baal et al.[59] Including the costs of healthcare during life years gained after TAVI compared with standard

treatment resulted in an increase in the ICER from £16,100 to £23,500 per QALY gained, changing TAVI from cost-effective to not cost-effective according to the UK cost per QALY threshold of £20,000.[59] A disadvantage of using health insurance claims data is that the reported cost estimates are expenditures reimbursed by health insurers based on agreements between healthcare providers and insurers, not actual costs. Therefore these are costs from a healthcare payer's perspective, instead of a societal perspective.

Costs outside healthcare can be divided in costs to patients and families (i.e. out-of-pocket payments, travel, time, and informal care costs) and costs in other sectors (e.g. productivity costs, costs of social care and support by municipalities, costs of education or costs of informal care).[34] In the early HTA of TEHV in the aortic position in elderly patients ***(Chapter 8)***, costs outside of healthcare included informal care and productivity costs. Informal care provided by family or friends is an important element of care for many patients, but can have a profound impact on the health and well-being of informal caregivers.[60] Therefore, the Dutch HTA guidelines prescribe the inclusion of costs of informal care in economic evaluations.[34] Informal care costs represented 6% and 17% of the total costs in SAVR and TAVI patients, respectively ***(Chapter 8)***. In addition to including costs of informal care, productivity costs of paid and unpaid work should be included in economic evaluations.[34] In ***Chapter 8***, 3% and 2% of the total costs after SAVR and TAVI with existing heart valve substitutes were productivity costs, respectively. This is smaller than in expensive drug costs where the productivity costs represented on average 24% of the total costs.[58] This is not surprising since we only included productivity costs of unpaid work due to the high age of the included patients. Nevertheless, unpaid work, such as babysitting or volunteer work, can be of high importance to the patients, family and friends, and society as a whole.

Data on informal care use and productivity of patients after heart valve implantations were collected with patient questionnaires ***(Chapter 6)***. The advantage of using patient questionnaires to collect data is that it is relatively easy and inexpensive to collect large amounts of real-world data.[61] However, the results of questionnaire studies can be subject to different types of bias such as non-response bias and social desirability bias.[61, 62] The response rate in ***Chapter 6*** was 56-59%. Non-responders were younger and more often female compared with responders. The influence of this bias on the outcomes is unclear. Healthier patients who were more capable to fill in the questionnaire may be overrepresented, but it is also possible that less healthy patients are overrepresented because healthier patients were too busy with work or other activities to participate. The impact of social desirability bias is expected to be low, because patients did not have direct contact with the interviewer when filling in the questionnaire. The other costs outside of healthcare (e.g. out-of-pocket payments and travel costs) were not expected to have large influence on the cost-effectiveness of

TEHV compared to existing heart valve substitutes. Unfortunately, we could not adopt a societal perspective in the early HTA of TEHV in the pulmonary position in children, because of limited data availability in the literature and unfeasibility to collect the required data ourselves due to the low annual number of children undergoing RVOTR.

To our knowledge, this thesis describes the first cost-effectiveness analysis of heart valve implantations from a societal perspective. An important question is how the chosen perspective could potentially affect decision-making. Including or excluding productivity costs can have a high impact on cost-effectiveness outcomes as shown by Krol et al. who found that including productivity costs of paid work altered decisions regarding reimbursement of expensive drugs in one-third of the cases compared to not including productivity costs.[58] In addition, in- or excluding informal care in cost-effectiveness analysis can result in large differences in cost-effectiveness outcomes.[63] In the early HTA of TEHV in the aortic position in elderly patients, including or excluding productivity and informal care costs would not have changed the reimbursement decision because TEHV were cost saving in both perspectives. However, the perspective did have impact on the magnitude of the cost savings ***(Chapter 8)***. The cost savings of SAVR with TEHV instead of bioprostheses were 9 times larger when applying a societal perspective (€639 per patients) instead of a healthcare perspective (€65 per patient) in the 'improved performance of TEHV' scenario. This is mainly caused by the reduction in productivity costs of unpaid work resulting from the reduction in valve-related events when using TEHV instead of bioprostheses (productivity costs savings with TEHV vs. bioprosthesis: €687 per patient). In TAVI patients, the cost savings of TEHV compared to bioprostheses were smaller when applying a societal perspective (€368 per patient) compared to a healthcare perspective (€415 per patient). This is caused by the higher increase of informal care costs due to longer life expectancy with TEHV compared to bioprostheses (TAVI: €193; SAVR €112 per patient) and smaller decrease of productivity costs due to prevention of valve-related events with TEHV compared to bioprostheses (TAVI: €145; SAVR: €687 per patient) in TAVI patients than in SAVR patients.

3. EARLY HEALTH TECHNOLOGY ASSESSMENT OF TEHV

This thesis includes early HTA studies of TEHV for two patient groups: aortic valve implantation in elderly patients ***(Chapter 8)*** and pulmonary valve implantation in children ***(Chapter 9)***. Both patient groups are important for different reasons. Elderly patients with aortic valve disease represent the largest target group for TEHV[4], whereas TEHV may be most beneficial in children with congenital heart disease who often suffer from pulmonary valve disease.[3] When comparing the early cost-effectiveness results

of both patient groups, the methodological differences, most importantly the different perspectives and time horizons, should be taken into account.

3.1 Cost-effectiveness results of singular improvements in TEHV performance components

The performance of TEHV was divided in three components: durability, thrombogenicity, and infection resistance. In both early HTA studies, improvements in durability had the largest impact on cost-effectiveness, while reductions in thrombogenicity had a negligible impact.

Durability

Preventing prosthetic valve dysfunction due to improved durability of TEHV can result in maximum QALY gains of 0.106 per patient during a time horizon of 10 years for children after RVOTR and 0.129 or 0.048 per patient during a lifetime horizon for elderly patients after SAVR or TAVI, respectively. These QALY gains were limited because the impact of re-interventions on health-related quality of life remains limited to a short recovery period of reduced health-related quality of life. It can be argued that preventing re-interventions, results in more benefits than can be expressed in QALYs. Most importantly reducing the probability of undergoing re-interventions may reduce anxiety of preparing for a re-intervention with a mortality risk, not only of patients but also of their family and friends. However, preventing re-interventions did not have a large impact on the other component of QALYs, length of life, because re-interventions were only associated with early mortality risks and did not influence the probability of other causes of death included in the model. This limited impact on life duration of preventing prosthetic valve dysfunction was even smaller in children after RVOTR because the risk of early mortality after re-intervention in these patients (2.6%) was lower than in elderly SAVR (9.0%) or TAVI (8.6%) patients. On the other hand, the cost savings of preventing re-interventions due to improved durability of TEHV were significant, with maximum cost savings of TEHV compared to existing heart valve substitutes of €20,568 per RVOTR patient, €1,420 per SAVR patient, and €578 per TAVI patient. The cost savings were especially high in children, because the probability of undergoing a re-intervention was considerably higher than in elderly patients.

Thrombogenicity

Preventing valve thrombosis due to reduced thrombogenicity of TEHV did not result in any QALY gains and minor cost savings in all patient groups (maximum cost savings with TEHV compared to existing heart valve substitutes: €43 per RVOTR patient, €102 per SAVR patient, and €122 per TAVI patient). This can be explained by the fact that most patients with valve thrombosis (88%) were treated with thrombolysis, which was associated with relatively low costs (€5,824) and utility impact (utility multiplier 0.968

applied for 10 days). However, more importantly, the occurrence of valve thrombosis with bioprostheses or allografts that were used for RVOTR, SAVR and TAVI in our target populations was low (10-year risk in children after RVOTR: 0.7%; lifetime risk after SAVR: 1.2% and TAVI: 1.3%).

Although thrombogenicity did not have a large impact on cost-effectiveness in the early HTA's of TEHV described in this thesis, reduced thrombogenicity of TEHV will probably yield larger benefits in patient groups that currently receive mechanical valves. Mechanical valves are often used in young adults and sometimes in middle-aged patients because of its longer durability and subsequent lower risk of reoperation.[64] However, they are associated with increased thrombogenicity, which means that there is an increased risk of valve thrombosis and thromboembolism (e.g. stroke). To lower these risks, patients are required to take anticoagulation medication during the rest of their lives. Unfortunately, this treatment is associated with increased bleeding risks, hassle of regulating anticoagulation medication, and risks of complications during pregnancy.[64] For example, a 45-year old, has a lifetime risk of thromboembolism of 18% and bleeding of 15%.[64] These risks can be reduced when TEHV have a low thrombogenicity and therefore lifelong anticoagulation treatment is not needed.

Infection resistance
Improvements in infection resistance did not have a large impact in children after RVOTR, because the occurrence of prosthetic valve endocarditis was relatively low. Prevention of prosthetic valve endocarditis in elderly patients only resulted in small cost savings in TAVI patients and even in costs increases in SAVR patients. This cost increase can be explained by increased healthcare and informal care costs during life years gained due to prevented prosthetic valve endocarditis, that could not be offset by reduction in healthcare and productivity costs. However, the number of QALYs gained due to improvements in infection resistance was enough to result in acceptable ICERs (ranging from €1,028-€2,222/QALY).

3.2 Cost-effectiveness results of combined improvements in TEHV performance components

In addition to modelling improvements in separate TEHV performance components, we also performed scenario analyses of improvements in more than one TEHV performance component simultaneously.

The perfect TEHV would reduce all risks of prosthetic valve-related events to the level in the general population, which is almost equal to zero. Although this perfect scenario is unrealistic, it does provide insight in the maximum health benefits and cost savings of TEHV. In the first 10 years after RVOTR in children, the maximum QALY gain of TEHV

compared to existing heart valve substitutes was 0.107 and the maximum cost savings were almost €21,000. If we could have applied a lifetime horizon in the early HTA of children after RVOTR, it is likely that the maximum QALY gain and cost savings would be higher, because more prosthetic valve-related events and re-interventions would have been prevented in the rest of the patient's lifetime. However, healthcare costs during life years gained would partly offset the cost savings of prevented re-interventions. The maximum lifetime QALY gain and cost savings of TEHV compared to bioprostheses were 0.249 QALYs and €1,344 per SAVR patient and 0.079, QALYs and €789 per TAVI patient. These cost savings are low when compared to the cost savings that can already be achieved in the first 10 years after RVOTR in children. This is mainly caused by the relatively low probability of re-intervention in elderly patients compared to children.

The 'improved performance' scenario represents a more realistic scenario where the occurrence of prosthetic-valve related events with TEHV was reduced with 50% compared to existing heart valve substitutes. In this scenario, using TEHV instead of existing heart valve substitutes resulted in QALY gains and cost savings in all patient groups.

In addition to the first two scenarios, we also modelled a 'partial improved' scenario, in which we explored whether a reduction in durability of TEHV compared to existing heart valve substitutes could be offset by reduction of thrombogenicity and improvement of infection resistance. Compared with elderly patients after SAVR or TAVI with bioprostheses, the partial improved performance of SAVR or TAVI with TEHV resulted in small QALY gains and cost increases, resulting in ICERs exceeding the cost-per-QALY-threshold of €20,000 in SAVR patients and €50,000 in TAVI patients. The impact of the 'partial improved' scenario was even worse in children after RVOTR, where there were reductions in QALYs and increases in costs, resulting in TEHV to be dominated by existing heart valve substitutes. These results emphasize the importance of improving durability of TEHV in order to be cost-effective compared to existing heart valve substitutes, especially in children in need of pulmonary valve replacement.

3.3 Headroom

The headroom is the maximum additional cost of a treatment over the comparator for which the new treatment would still be considered cost-effective.[65] If there is little or no chance that the new treatment could be marketed at a price below the headroom, then the intervention should not attract further investment.[65] Assuming improved but not perfect performance of all components, the headroom of TEHV was around €3,200 for SAVR in elderly patients , €1,200 for TAVI in elderly patients, and almost €12,000 for RVOTR in children. These numbers represent the additional costs of TEHV in addition to the costs of existing biological heart valve substitutes (i.e.

€2,500 for surgical bioprostheses, €18,000 for transcatheter bioprostheses and €5,000 for allografts and Contegras). The exact costs of TEHV are not known yet, but we may assume that the costs will be comparable to other inorganic heart valve substitutes (i.e. mechanical valves, €1,500). Considering the expected relatively low expected manufacturing costs of TEHV, the results of the headroom analyses are promising for the commercial viability of TEHV in the Netherlands.

The cost-per-QALY threshold that was used to calculate the headroom was based on the disease burden determined with the proportional shortfall method.[66] However, the appropriateness of this method in children can be criticised. Due to the relative nature of proportional shortfall, this method gives a higher weight to older patients losing QALYs than younger patients losing the same amount of QALYs.[67] For example, a 5-year old losing 21 QALYs loses 31% of the expected QALYs without disease, while a 50-year old losing 21 QALYS loses 75% of the expected QALYs without disease. According to Reckers et al. this is not in line with the stronger societal preference of providing healthcare to younger rather than to older patients.[68] Therefore, the societal willingness to pay for an additional QALY in children in need of RVOTR might be higher, resulting in an even higher headroom for TEHV in this patient group.

3.4 Budget impact

The budget impact analyses in ***Chapter 8 and 9*** addressed the expected changes in the expenditure of the Dutch healthcare system after the adoption of TEHV. Assuming that TEHV will have improved performance compared to existing heart valve substitutes, the introduction of TEHV will lead to cost savings of the Dutch healthcare budget. The magnitude of these cost savings depends on the exact performance of TEHV. In the 'improved performance' scenario, large cost savings can be realized in the first 10 years after adoption of TEHV varying between €2.8-€11.2 million in SAVR patients, €3.2-€12.8 million in TAVI patients, and €1.9-€7.5 million in RVOTR patients, depending on the substitution rate of TEHV. The high cost savings in elderly patients requiring aortic valve implantation are mainly caused by the high number of patients, since individual cost savings are relatively low. In contrast, the cost savings expected in the relatively small population of children requiring pulmonary valve replacement are high because of the high expected cost savings per patient.

3.5 Uncertainties in early HTA

A challenge inherent to early HTA is the uncertainty of the exact application and the outcomes in terms of costs and effects of the new intervention. TEHV developers aim to implement TEHV in the pulmonary position first due to lower performance requirements in the right side of the heart, followed by the aortic position, but it is uncertain whether these will indeed be the first applications of TEHV. In addition,

it still needs to be determined whether TEHV will be implanted percutaneously (i.e. transcatheter valve implantation) or surgically. Furthermore, since the first clinical trials in humans have only recently started, it is currently unclear whether TEHV can indeed grow with the body and last a lifetime and whether TEHV will also function in patients with comorbidities.[2] While these uncertainties exist, it is important to explore many possible scenarios in an early HTA. Therefore, we have investigated the cost-effectiveness of TEHV in the aortic position compared to surgical aortic valve replacement, as well as transcatheter aortic valve implantation. Since transcatheter pulmonary valve implantation is not the current standard practice in children, this approach was not considered as comparator in the early HTA of TEHV in the pulmonary position in children. The uncertainty around the performance of TEHV was addressed by performing many scenario analyses with varying performance of TEHV. The results can provide the developers of TEHV guidance in the focus of their research.

In addition to uncertainty related to the intervention under development in early HTA, there are two types of uncertainty that are important in every decision-analytic model. First, structural or model uncertainty, which relates to the assumptions imposed by the modeling framework. In this thesis, we have tried to reduce this uncertainty by systematically developing a conceptual model informed by existing models and expert opinion. Second, parameter uncertainty is the uncertainty around the input parameters of the model. This type of uncertainty can be explored in deterministic and probabilistic sensitivity analyses. In a deterministic sensitivity analysis (DSA), parameter values are varied manually to test the sensitivity of the model's results to changes in specific parameters or sets of parameters. The scenario analyses with varying performance of TEHV are DSAs. In a probabilistic sensitivity analysis (PSA), all parameters are varied simultaneously, with multiple sets of parameter values being sampled from a priori defined probability distributions. The PSA results in ***Chapter 8 and 9*** showed that, although there was substantial uncertainty in the input parameters, the probability that TEHV are cost-effective compared to existing heart valve substitutes was very high (99-100%) in all patient populations studied in this thesis when the performance of TEHV is improved with 50% in all components compared to existing heart valve substitutes. This implies that when TEHV can achieve considerable improvements in valve performance, there is high certainty that TEHV are cost-effective compared to existing heart valve substitutes, despite the uncertainty around the input parameters. However, to be able to estimate the exact cost-effectiveness more precisely, uncertainty around the input parameters should be reduced.

4. IMPLICATIONS FOR DIFFERENT STAKEHOLDERS

Since TEHV are currently in the development phase, this thesis has the most implications for developers of TEHV. The systematic reviews and meta-analysis performed in this thesis can be used as a benchmark for the minimum performance requirements of TEHV. As long as TEHV indeed result in improved performance compared to existing heart valve substitutes, the maximum additional costs of TEHV in order to be cost-effective (i.e. the headroom) seem sufficient for TEHV to be commercially viable. Finally, we concluded that the success of the application of TEHV in the aortic position in elderly and in the pulmonary position in children mostly depends on the improvements in durability compared to existing heart valve substitutes.

In ***Chapter 10***, three perspectives on balancing risks and benefits of different treatment options in structural heart disease were discussed. In addition to the developers perspective described above, the implications of this thesis can also be viewed from these different perspectives.

From a clinical perspective, it is important to have reliable prognostic models that help clinicians to determine the optimal treatment option and the optimal timing of this (re-) intervention. The results of the early HTA informs clinicians about the potential benefits of TEHV. This early introduction to TEHV as possible alternative for existing heart valve substitutes may result in faster adoption of TEHV in clinical practice.[37] Furthermore, the decision-analytic model developed in this thesis can inform clinicians about the life expectancy and lifetime risks on valve-related events in specific patient groups with existing heart valve substitutes. However, it needs to be noted that the current decision-analytic model cannot be used to predict outcomes or make treatment decisions for individual patients. More patient-level data is needed to be able to adjust the model predictions, especially the long-term clinical outcomes, to specific patient and intervention characteristics.

From a patient perspective, it is important that treatment decisions are the result of a shared decision making process between patients and clinicians. In shared decision making, not only the magnitude of risks and benefits are taken into account, but also the patient's values in relation to these risks.[18, 20] Previous research has shown that many patients have limited knowledge of the advantages and disadvantages of existing heart valve substitutes and experience difficulties in choosing a heart valve substitute. [69] In response to these findings, the researchers developed a patient decision aid for prosthetic heart valve selection.[70] This patient decision aid did not make the prosthetic heart valve selection easier, but it did improve patients' knowledge, made them feel better informed, less anxious and depressed, and improved mental quality of

life at the time of decision making.[70] The results of the systematic reviews and meta-analyses of existing heart valves reported in this thesis can be used to complement and update the information in the patient decision aid. Furthermore, it can inform patients about the potential benefits of TEHV.

From a societal perspective, it is desirable to allocate the limited resources for healthcare in a way that maximises the health of the overall population by avoiding the implementation of comparatively ineffective or inefficient interventions.[33] Healthcare decision makers strive to achieve this optimal allocation. Health Technology Assessment studies can support them in making these reimbursement decisions. ***Chapter 8 and 9*** of this thesis have shown that it is likely that implementing TEHV will lead to improved health at acceptable or even lower costs. Further, healthcare decision makers would like to know what impact implementing a new intervention has on the total healthcare budget. The analysis of the impact on the healthcare budget in ***Chapter 8 and 9*** showed that implementing TEHV as an alternative heart valve substitute is expected to result in considerable cost savings, once this option moves into a clinical stage.

5. CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

This thesis investigated the potential cost-effectiveness of TEHV that are currently in an early development phase and not yet implemented in clinical practice. The early HTA analyses indicated that developers of TEHV should especially focus on increasing durability of TEHV compared to existing heart valves, as this had the most impact on cost-effectiveness in all patient groups. Furthermore, our results suggest that TEHV are likely to be cost-effective compared to existing heart valve substitutes in both the aortic position in elderly patients and the pulmonary position in children. On an individual patient level, TEHV will probably yield more QALY gains and save more costs in children in need of pulmonary valve implantation than in elderly patients requiring aortic valve implantation, due to the high probability of re-intervention in children. However, the large size of the patient population makes elderly patients with aortic valve disease an important target population with high potential benefits and cost savings on a population level. This means that from a societal perspective, it is worthwhile to introduce TEHV as an alternative heart valve substitute in both patient populations.

In the future, the model developed in this thesis can be updated when more evidence on the performance of TEHV is generated to provide up-to-date estimates of the cost-effectiveness of TEHV. These updated outcomes can guide developers in priority

setting of further research initiatives regarding the development of TEHV. Furthermore, the model can be adapted to other healthcare settings to estimate the potential cost-effectiveness of TEHV in other countries or regions in the world. Finally, when TEHV are ready for introduction in clinical practice, the model can be used to inform healthcare decision makers on the cost-effectiveness and budget impact of TEHV in reimbursement decision making.

Although the decision-analytic model described in this thesis was mainly used for the early HTA of TEHV, there are many other applications of this model possible. In this thesis, we have already used this model in systematic reviews and meta-analyses to translate the results into estimates of life expectancy and lifetime risks on events to make the results easier to understand by patients and clinicians. Future systematic reviews and meta-analyses can also use this model to translate their results to lifetime estimates. In addition, other possible applications of the model are cost-effectiveness analyses of other heart valve implantations, such as SAVR versus TAVI or mechanical versus bioprostheses.

Finally, improvements can be made in the modelling of outcome after heart valve implantations, such as using time-varying hazards of valve-related events where appropriate, taking into account dependence of clinical outcomes on patient and intervention characteristics and previous events, and applying a lifetime horizon in cost-effectiveness analyses considering heart valve replacements in children, young adults and middle aged patients. In addition, further external validation of the outcomes is necessary to enhance the confidence in the model results.

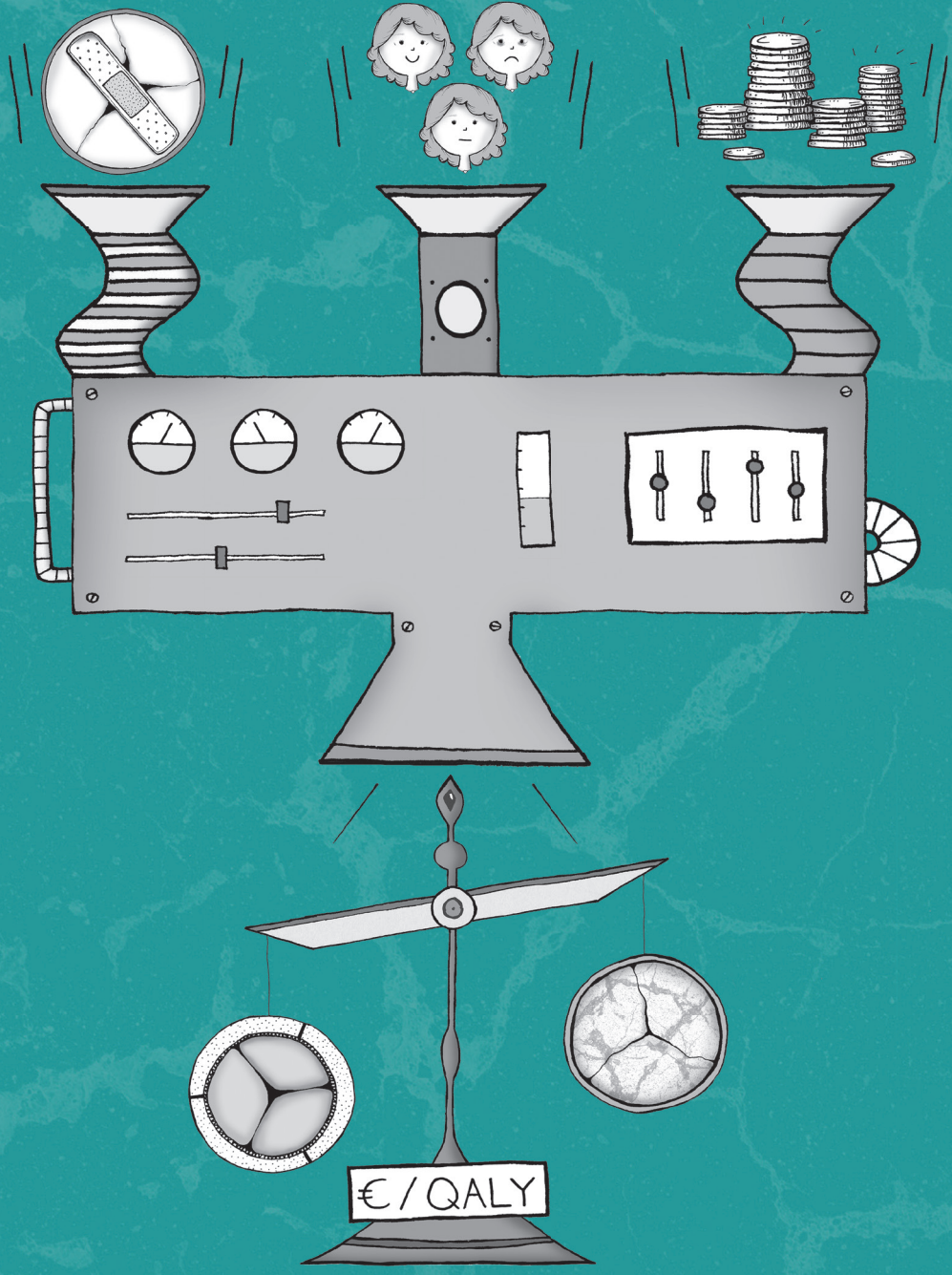
'Will tissue-engineered heart valves change the world?' was the question posed in *Nature Clinical Practice Cardiovascular Medicine* in 2005. The authors concluded that TEHV have the potential to increase life expectancy, reduce valve-related events, improve quality of life and be affordable worldwide.[21] This thesis indicated that these are realistic expectations. Moreover, it described methods that can be re-used in the future whenever additional evidence becomes available to further answer the question if TEHV will change the world.

REFERENCES

1. Hsu, C.-C. and B.A. Sandford, *The Delphi technique: making sense of consensus.* Practical Assessment, Research & Evaluation, 2007. **12**(10): p. 1-8.
2. Hein, R., et al., *Outcome of patients after emergency conversion from transcatheter aortic valve implantation to surgery.* EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology, 2013. **9**(4): p. 446-451.
3. Arsalan, M., et al., *Predictors and outcome of conversion to cardiac surgery during transcatheter aortic valve implantation.* European Journal of Cardio-Thoracic Surgery, 2018.
4. Siebert, U., et al., *State-transition modeling: a report of the ISPOR-SMDM modeling good research practices task force-3.* Value in Health, 2012. **15**(6): p. 812-820.
5. Karnon, J., et al., *Modeling Using Discrete Event Simulation A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force–4.* Medical Decision Making, 2012. **32**(5): p. 701-711.
6. Rothwell, P., et al., *Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study).* The Lancet, 2005. **366**(9499): p. 1773-1783.
7. De Feo, M., et al., *Mechanical valve prosthesis is a valid option for aortic valve replacement in the elderly.* J Heart Valve Dis, 2004. **13**(1): p. 103-108.
8. Huygens, S.A., et al., *How much does a heart valve implantation cost and what are the health care costs afterwards?* Open Heart, 2018. **5**(1).
9. Ioannidis, J.P. and J. Lau, *Pooling research results: benefits and limitations of meta-analysis.* The Joint Commission journal on quality improvement, 1999. **25**(9): p. 462-469.
10. Mokhles, S., J.J. Takkenberg, and T. Treasure, *Evidence-based and personalized medicine. It's [AND] not [OR].* The Annals of thoracic surgery, 2017. **103**(1): p. 351-360.
11. Blackstone, E.H., D.C. Naftel, and M.E. Turner Jr, *The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information.* Journal of the American Statistical Association, 1986. **81**(395): p. 615-624.
12. Blackstone, E.H. and J.W. Kirklin, *Death and other time-related events after valve replacement.* Circulation, 1985. **72**(4): p. 753-767.
13. Zorginstituut, N., *Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg.* Diemen: Zorginstituut Nederland, 2015.
14. Eddy, D.M., et al., *Model Transparency and Validation A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force–7.* Medical Decision Making, 2012. **32**(5): p. 733-743.
15. Opić, P., et al., *Psychosocial functioning of adults with congenital heart disease: outcomes of a 30–43 year longitudinal follow-up.* Clinical Research in Cardiology, 2015. **104**(5): p. 388-400.
16. Chen, X.J., et al., *Bioprosthetic pulmonary valve replacement: Contemporary analysis of a large, single-center series of 170 cases.* J Thorac Cardiovasc Surg, 2013. **146**(6): p. 1461-1466.
17. Mokhles, M.M., et al., *Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit.* European Journal of Cardio-Thoracic Surgery, 2011. **40**(3): p. 571-578.

18. Knowles, R.L., et al., *Patient-reported quality of life outcomes for children with serious congenital heart defects.* Archives of disease in childhood, 2014: p. archdischild-2013-305130.
19. Heijink, R., et al., *Decomposing cross-country differences in quality adjusted life expectancy: the impact of value sets.* Population health metrics, 2011. **9**(1): p. 1.
20. van Nooten, F., et al., *What should we know about the person behind a TTO?* 2018, Springer.
21. Essers, B. *An investigation of age dependency in Dutch values for EQ-5D-Y*. in *12th European Conference on Health Economics*. 2018. Maastricht.
22. Krol, M., et al., *A noticeable difference? Productivity costs related to paid and unpaid work in economic evaluations on expensive drugs.* The European Journal of Health Economics, 2016. **17**(4): p. 391-402.
23. Baal, P., D. Meltzer, and W. Brouwer, *Future costs, fixed healthcare budgets, and the decision rules of cost-effectiveness analysis.* Health economics, 2014.
24. Hoefman, R.J., J. van Exel, and W. Brouwer, *How to include informal care in economic evaluations.* Pharmacoeconomics, 2013. **31**(12): p. 1105-1119.
25. Swanborn, P.G., *Basisboek sociaal onderzoek*. 2010: Boom onderwijs.
26. Edwards, P., et al., *Increasing response rates to postal questionnaires: systematic review.* Bmj, 2002. **324**(7347): p. 1183.
27. Krol, M., J. Papenburg, and J. van Exel, *Does including informal care in economic evaluations matter? A systematic review of inclusion and impact of informal care in cost-effectiveness studies.* Pharmacoeconomics, 2015. **33**(2): p. 123-135.
28. Nkomo, V.T., et al., *Burden of valvular heart diseases: a population-based study.* The Lancet, 2006. **368**(9540): p. 1005-1011.
29. Kumar, P.C., M, *Clinical Medicine*. 8 ed. 2012: Elsevier.
30. Korteland, N.M., et al., *Mechanical aortic valve replacement in non-elderly adults: meta-analysis and microsimulation.* European Heart Journal, 2017: p. ehx199.
31. Cosh, E., et al., *Investing in new medical technologies: A decision framework.* Journal of Commercial Biotechnology, 2007. **13**(4): p. 263-271.
32. Zwaap, J., et al., *Kosteneffectiviteit in de praktijk*. 2015, Zorginstituut Nederland.
33. Reckers-Droog, V., N. van Exel, and W. Brouwer, *Looking back and moving forward: On the application of proportional shortfall in healthcare priority setting in the Netherlands.* Health Policy, 2018.
34. Reckers-Droog, V., J. van Exel, and W. Brouwer, *Who should receive treatment? An empirical enquiry into the relationship between societal views and preferences concerning healthcare priority setting.* PloS one, 2018. **13**(6): p. e0198761.
35. Bouten, C.V., A. Smits, and F. Baaijens, *Can we Grow Valves Inside the Heart? Perspective on Material-based In Situ Heart Valve Tissue Engineering.* Frontiers in Cardiovascular Medicine, 2018. **5**: p. 54.
36. Buisman, L.R., et al., *The Early Bird Catches the Worm: Early Cost-Effectiveness Analysis of New Medical Tests.* International journal of technology assessment in health care, 2016: p. 1-8.
37. Baumgartner, H., et al., *2017 ESC/EACTS Guidelines for the management of valvular heart disease.* European heart journal, 2017. **38**(36): p. 2739-2791.

38. Nishimura, R.A., et al., *2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines.* Circulation, 2017. **135**(25): p. e1159-e1195.
39. Korteland, N.M., et al., *Prosthetic aortic valve selection: current patient experience, preferences and knowledge.* Open Heart, 2015. **2**(1): p. e000237.
40. Korteland, N.M., et al., *Does the use of a decision aid improve decision making in prosthetic heart valve selection? A multicenter randomized trial.* Circulation: Cardiovascular Quality and Outcomes, 2017. **10**(2): p. e003178.
41. Siebert, U., *When should decision-analytic modeling be used in the economic evaluation of health care?* Eur J Health Econom, 2003. **3**: p. 143.
42. Yacoub, M.H. and J.J.M. Takkenberg, *Will heart valve tissue engineering change the world?* Nat Clin Pract Cardiovasc Med, 2005. **2**(2): p. 60-61.


€ / QALY

12

Summary
Samenvatting
About the author
PhD Portfolio
List of publications
Dankwoord

SUMMARY

Background
Heart valve disease represents a major global health burden. One of the main treatment options for heart valve disease is heart valve replacement with a biological or mechanical heart valve substitute. Existing heart valve substitutes all have their limitations; biological valves have a limited durability with subsequent risk of re-intervention, while mechanical valves are associated with the need of lifelong anticoagulation medication with subsequent risks of bleeding and complications during pregnancy. One of the most promising recent endeavours to solve these problems is the creation of living heart valves through the process of tissue engineering. In this approach, a valve-shaped scaffold implanted in the heart of the patients recruits cells from the bloodstream and surrounding tissues and gradually transforms into a valve while the scaffold degrades. Both surgical and transcatheter implantation of tissue-engineered heart valves (TEHV) are currently explored. TEHV have the potential to reduce or even eliminate the limitations of existing heart valve substitutes. In contrast to existing heart valve substitutes, TEHV are living heart valve prostheses with growth potential. Therefore, re-interventions because patients outgrow the heart valve substitute may no longer occur. In addition, and in contrast to biological valves, they would ideally last a lifetime in the same way as most native heart valves do *(durability)*. Furthermore, and in contrast to mechanical valves, the risk of thromboembolic events is expected to be low and therefore lifelong anticoagulation may not be required *(thrombogenicity)*. Finally, TEHV may be more resistant to infection of the heart valve, since the heart valve substitute is made of the patient's own tissue *(infection resistance)*.

This thesis describes the early Health Technology Assessment (HTA) of TEHV. HTA is the systematic evaluation of social, economic, organizational and ethical issues of a health intervention to inform policy decision making. An important component of HTA is the economic evaluation in which alternative treatment options are compared in terms of their costs and consequences. Economic evaluations can support healthcare decision makers in allocating the limited healthcare budget in a way that maximizes the health of the overall population and avoids implementation of comparatively ineffective or inefficient healthcare interventions. HTA is often performed when a new healthcare intervention is ready for introduction in clinical practice. However, information on cost-effectiveness can also be valuable earlier in the development process. Early HTA is the use of economic evaluation in early stages of the development of new healthcare interventions mainly to guide developers at the time that investment decisions are made, for example by investigating the optimal target population. In addition, patients, clinicians and healthcare decision makers can benefit from timely information on the

(cost-)effectiveness of potential interventions that may become available in clinical practice in the future.

Model development

To be able to perform early HTA of TEHV, we needed a decision-analytic model that could synthesize evidence from different sources on costs and effects of heart valve implantations. The development of this model is described in the first part of this thesis. One of the first steps of model development, reviewing existing models addressing related problems, is described in **Chapter 2**. This chapter describes the systematic review of model-based economic evaluations of heart valve implantations. This study showed that the methodological quality of currently published model-based economic evaluations of heart valve implantations can be improved by providing more detailed descriptions of sources of input parameters and modelling methods, and using direct utility assessment with a preference-based quality of life instrument instead of indirect utility assessment using New York Heart Association (NYHA) class. Furthermore, this review showed that that there is room for patient-simulation models considering the cost-effectiveness of heart valve implantations in other valve positions besides the aortic valve performed from a societal perspective.

The development of the conceptual model is described in **Chapter 3**. This conceptual model served as the foundation for the decision-analytic model that was used in this thesis. The development started with scoping of the decision problem and developing a draft conceptual model within a small workgroup. In this draft conceptual model, the strengths and limitations of existing economic models of heart valve implantations and the opportunities for future models described in **Chapter 2** were taken into account. This draft conceptual model was discussed with a Delphi panel of ten experts, including cardiothoracic surgeons, cardiologists and a biomedical scientist. This resulted in a conceptual model reflecting the most important consequences after heart valve interventions based on the views of a multidisciplinary group of experts. In the conceptual model, the patient is followed from the time of the heart valve implantation until death. Patients can survive the intervention or not (i.e. early mortality). When patients survive the intervention, they can remain alive, die from non-valve related causes (i.e. background and excess mortality), or experience a valve-related event. The following events were included during the entire simulation: stroke, bleeding, prosthetic valve dysfunction (structural valve deterioration and non-structural valve dysfunction), -thrombosis and -endocarditis. In addition, the following events were only included within 30 days after the intervention: myocardial infarction, vascular complication, arrhythmias/atrial fibrillation, pacemaker implantation, renal failure/ acute kidney injury. Patients experiencing an event can die or survive the event. When

patients survive the event they can stay alive, experience another event or die due to non-valve related causes.

Health outcomes and costs of existing heart valve substitutes

Before we could use our decision-analytic model for the early HTA of TEHV, data needed to be collected on the input parameters of the model: risks of mortality and morbidity, health-related quality of life, and societal costs. Since TEHV are not yet implemented in clinical practice, assumptions had to be made about their performance and costs. On the other hand, the performance and costs of existing heart valve substitutes could be based on evidence from clinical practice, which is reviewed in the second part of this thesis.

This thesis includes three systematic reviews and meta-analyses of clinical outcomes after heart valve implantations, two on the outcomes after surgical aortic valve replacement (SAVR) and one on the outcomes after right ventricular outflow tract reconstruction (RVOTR; i.e. surgical pulmonary valve replacement).

Chapter 4 describes the systematic review and meta-analysis of outcomes after SAVR with biological valves: allografts (human donor) and bioprostheses (animal donor). The results showed that patients receiving allografts were younger (mean age: 48.8 vs. 71.8 years) and less often had concomitant coronary artery bypass grafting (CABG) (11.9 vs. 40.0%) than patients receiving bioprostheses. Early mortality after SAVR with bioprostheses and allografts was approximately 5%. The most often occurring valve-related event was thromboembolism after SAVR with bioprostheses (1.0%/year) and structural valve deterioration (SVD) after SAVR with allografts (1.1%/year). Re-interventions occurred most often for SVD.

Chapter 5 presents the systematic review and meta-analysis on outcomes after SAVR with bioprostheses in elderly patients. The results of the meta-analysis were translated to estimates of life expectancy and lifetime risks on events using our decision-analytic model. As expected, the pooled estimates of early mortality risk (5.4 vs. 5.0%) and linearized occurrence rates of most late events (non-structural valve dysfunction 0.5 vs. 0.2 %/year; thromboembolism 1.8 vs. 1.1%/year; bleeding 0.8 vs. 0.4%/year; endocarditis 0.6 vs. 0.4%/year) were higher, while the linearized occurrence rates of SVD (0.4 vs. 0.5%/year) and re-intervention (0.6 vs. 0.7%/year) after SAVR with bioprostheses were lower in elderly patients than in patients of all ages (**Chapter 4**). The relatively low occurrence of SVD (lifetime risk 7.2% in 75-year olds and 2.8% in 85-year olds) and re-intervention (lifetime risk 8.8% in 75-year olds and 4.2% in 85-year olds) confirms the recommendation in clinical guidelines to use bioprostheses instead of mechanical prostheses in elderly patients in need of aortic valve replacement. The

life expectancy of patients after SAVR with bioprostheses was comparable to the age and sex matched general population, which is probably caused by the careful selection of relatively healthy elderly to undergo SAVR, while frail elderly are rejected for surgery.

Chapter 9 describes the systematic review and meta-analysis of RVOTR in children. In most patients younger than two years old at the time of surgery, the etiology was truncus arteriosus communis (TAC; 66.5%) followed by tetralogy of Fallot (TOF, 14.6%). The pulmonary valve was mostly replaced with biological valves (allografts 61.2% or bioprostheses 38.7%) instead of mechanical valves because the risk of valve thrombosis associated with mechanical valves in the pulmonary position is higher than in the aortic position. In contrast, most patients above two years old at the time of surgery had TOF (42.5%) followed by TAC (13.1%) and the pulmonary valve was replaced with allografts (42.1%), bioprostheses (40.3%), or synthetic polytetrafluorethylene (PTFE; 17.1%) prostheses. Early mortality was higher in children below two years old than in those above two years old (11.0% vs. 4.7%). In addition, the re-intervention risk of children below two years old was considerably higher than in children above two years old (five-year freedom from re-intervention 46.1% in age ≤2 years vs. 81.1% age >2 years at RVOTR), while other late events were not reported to occur in the younger children.

The impact of heart valve implantations goes beyond the clinical outcomes in terms of mortality and morbidity. This impact is investigated in **Chapter 6**, which presents the results of a questionnaire measuring patient-reported health-related quality of life, informal care use and productivity of patients after SAVR (n=633), TAVI (n=257), or RVOTR (n=26). The results showed that patients after aortic and pulmonary valve implantations experienced relatively mild limitations in daily life compared to the age and sex matched general population. On average, SAVR and TAVI patients had a lower health-related quality of life than the general population, while RVOTR patients had a slightly higher health-related quality of life than the general population. More specifically, patients reported poorer health-related quality of life on physical health domains than the general population, while their scores were comparable or slightly better on mental health domains. Further, patients reported to use informal care more frequently, but the amount of informal care provided per patient was lower than among the users of informal care in the general population. Finally, the labor participation of patients was comparable to the general population. The vast majority of elderly SAVR and TAVI patients did not have paid employment, but more than one third of these patients reported to perform unpaid work activities (e.g. volunteer work or babysitting).

Chapter 7 describes the retrospective analyses of Dutch health insurance claims data of patients who had undergone heart valve implantations in the years 2010 to 2013 (n=18,903) and controls (n=188,925). In this study, costs of heart valve implantations, treatment of complications, and healthcare use in- and outside hospitals in the years following heart valve implantations were assessed for four age groups. The mean costs of the heart valve implantations considered in this thesis were €25,165 for SAVR and €32,209 for TAVI in elderly patients and €21,800 for RVOTR in children. Re-interventions were associated with the highest healthcare costs (comparable to initial intervention costs). In-hospital antibiotic treatment for prosthetic valve endocarditis has the second highest healthcare costs (on average €8,069 for children after RVOTR and €8,923 in elderly patients after aortic valve implantation). Thrombolytic therapy for prosthetic valve thrombosis had the lowest costs of all prosthetic valve related events (€5,824). Multilevel generalized linear models showed that older age, female gender, comorbidities, low socioeconomic status, and complications were associated with increased annual healthcare costs in patients after heart valve implantations. The total healthcare costs of patients after heart valve implantations were compared with total healthcare costs of controls from the general population with comparable age, sex, comorbidities and socioeconomic status. In the three years following the heart valve implantation, healthcare costs of patients were higher than in controls, especially in the year of implantation (children €11,766 vs. €796, young adults €15,060 vs. €2,944, middle aged €16,104 vs. €4,612, and elderly €18,255 vs. €9,236). But also in the following years, healthcare costs of patients were higher than in controls, especially in children (year 2 €5,495 vs. €802; year 3 €5,015 vs. €786). In elderly patients, the costs of nursing homes were lower in SAVR patients than in the general population (€866 in year 1, €1,763 in year 2 and €1,990 in year 3 after the heart valve implantation versus €2,761 per year in controls), reflecting the selection of relatively healthy elderly (and therefore not living in nursing homes) to undergo SAVR.

Early Health Technology Assessment of TEHV

The third part of this thesis describes the early HTA of TEHV using the patient-level simulation model and input parameters described in the previous parts of this thesis. We focused on the use of TEHV in the aortic and pulmonary position. In the aortic position, we focused on elderly patients because the prevalence of aortic valve disease is the highest in these patients, due to degeneration of the native aortic valve **(Chapter 8)**. In the pulmonary position, we focused on children because pulmonary valve disease is often caused by congenital heart valve disease **(Chapter 9)**. In both studies, we estimated the cost-effectiveness, budget impact, and headroom of TEHV compared to existing heart valve substitutes using various scenarios for the performance of TEHV. The performance of TEHV was divided into three components: durability, thrombogenicity, and infection resistance. In both patient groups, improvement in durability was the

most important driver of QALY gain and cost savings (ranging from 0.049-0.152 QALY and €118-€634 per SAVR patient, 0.023-0.074 QALY and €156-€586 per TAVI patient, and 0.031-0.083 QALY and €5,691-€20,568 per RVOTR patient for small improvements in durability to optimal durability of TEHV). Moreover, the headroom (i.e. the maximum increase in the price of TEHV compared to the price of existing heart valve substitutes) was sufficiently large for TEHV to be economically viable. The headroom varied from €38 per surgical aortic TEHV, €35 per transcatheter aortic TEHV, and €12 per pulmonary surgical TEHV if TEHV would only result in a small reduction in thrombogenicity to €6,323 per surgical aortic TEHV, €4,734 per transcatheter aortic TEHV, and €23,041 per pulmonary surgical TEHV if there would be no prosthetic valve related events at all using TEHV. The most individual benefits may be gained in children undergoing pulmonary valve replacement (i.e. right ventricular outflow tract reconstruction; RVOTR) with TEHV because the probability on re-intervention with existing heart valve substitutes is high and associated with high costs. However, the number of patients undergoing RVOTR in the Netherlands is small (85 RVOTR/year). Assuming 'improved performance' of TEHV (-50% prosthetic valve-related events), the national cost savings in the next 10 years ranged from €1.9 million when 25% of RVOTR was performed with TEHV to €7.5 million when all RVOTR were performed with TEHV instead of existing heart valve substitutes. The individual benefits that may be gained by using TEHV in elderly patients undergoing aortic valve implantation (SAVR or TAVI) were smaller, because the risk of re-intervention with currently used bioprostheses was low in these patients. However, the relatively small individual QALY gains and cost savings with TEHV in elderly patients can result in large national health care savings due to the relatively large size of this patient population (1,931 SAVR/year; 809-3,745 TAVI/year). The national cost savings in the next 10 years of TEHV with 'improved performance' (-50% of prosthetic valve-related events) ranged between €2.8 million (SAVR) and €3.2 million (TAVI) when 25% of heart valve implantations was performed with TEHV to €11.2 million (SAVR) and €12.8 million (TAVI) when all heart valve implantations were performed with TEHV instead of bioprostheses.

Discussion and conclusion

Chapter 10 discusses how decision making in structural heart disease could be optimized from three perspectives. From a clinical perspective, decision making can be optimized by developing and using novel prognostic models that are able to simultaneously combine several longitudinally collected data during patient follow-up with these patients' outcome. From a patient perspective, supporting shared decision making by implementing patient information portals and decision aids will empower and serve the individual patient in balancing risks and benefits. From a societal perspective, information on cost-effectiveness should be used by policy makers

making funding decisions to avoid the reimbursement of comparatively ineffective or inefficient healthcare interventions.

Finally, in **Chapter 11**, the three lines of research in this thesis, implications of our results for different stakeholders, and recommendations for further research were discussed. We concluded that this thesis provided valuable information for different stakeholders. First, it informs biomedical companies developing TEHV about minimum performance requirements and maximum additional costs of TEHV in different target populations, which can guide priority setting of further research initiatives. Developers of TEHV should especially focus on improving durability of TEHV compared to existing heart valve substitutes, since this was the largest driver of QALY gains and cost savings. However, it was noted that the potential improvement in thrombogenicity of TEHV compared to existing heart valve substitutes is expected to result in larger benefits in other patient populations than discussed in this thesis (i.e. young adults or middle-aged patients eligible for mechanical heart valve substitutes). Moreover, the headroom was sufficiently large for TEHV to be economically viable. Second, it provides patients and clinicians with the first estimates of potential improvements in clinical outcomes with TEHV, which may result in faster adoption of TEHV in clinical practice. Finally, it informs healthcare payers about the possible entrance of TEHV to the market, the promising potential cost-effectiveness of TEHV and the expected large cost savings for the national healthcare budget, which may result in more timely decisions about reimbursement.

SAMENVATTING

Achtergrond

Hartklepaandoeningen zorgen wereldwijd voor veel gezondheidsverlies. Een van de belangrijkste behandelmogelijkheden voor hartklepaandoeningen is een hartklepvervanging met een biologische of mechanische hartklepprothese. De bestaande hartklepprotheses hebben allemaal hun eigen beperkingen. Biologische kleppen hebben een beperkte levensduur, waardoor op termijn een re-interventie nodig kan zijn. Daarentegen is bij mechanische kleppen levenslang gebruik van antistollingsmedicatie noodzakelijk, waardoor patiënten een verhoogde kans hebben op bloedingen en complicaties tijdens een zwangerschap. Een van de meest veelbelovende ontwikkelingen om deze problemen te verhelpen is het creëren van een levende hartklep met behulp van 'tissue engineering'. Bij deze methode wordt een mal in de vorm van een hartklep in het hart van de patiënt geplaatst. Deze mal trekt vervolgens cellen aan uit de bloedsomloop en omliggend weefsel die geleidelijk veranderen in een hartklep, terwijl de mal afbreekt. Zowel chirurgische als transkatheter implantatie van tissue-engineered hartkleppen (TEHK) worden momenteel onderzocht. TEHK hebben de potentie om de nadelen van bestaande hartklepprotheses te beperken of zelfs te verhelpen. TEHK zijn levende hartkleppen en hebben daarom de potentie om, in tegenstelling tot bestaande hartklepprotheses, mee te groeien met de patiënt. Daarom zullen re-interventies bij patiënten die hun hartklepprothese ontgroeid zijn mogelijk niet nodig zijn. Idealiter zullen zij een leven lang mee gaan, in tegenstelling tot biologische hartklepprotheses (*duurzaamheid*). Daarnaast wordt verwacht dat het risico op trombo-embolieën laag is, waardoor de levenslange antistolling die noodzakelijk is bij mechanische hartklepprotheses mogelijk niet nodig is *(trombogeniciteit)*. Ten slotte is het mogelijk dat TEHK beter bestand zijn tegen infectie van de hartklep, omdat de hartklepprothese gemaakt is van het eigen lichaamsweefsel van de patiënt *(infectie resistentie)*.

Dit proefschrift beschrijft de vroege Health Technology Assessment (HTA) van TEHK. HTA is de systematische evaluatie van sociale, economische, organisatorische en ethische vraagstukken omtrent een gezondheidsinterventie. De resultaten kunnen gebruikt worden bij het nemen van beleidsbeslissingen. Een belangrijke component van HTA is de economische evaluatie. In een economische evaluatie worden de kosten en effecten van alternatieve behandelmogelijkheden met elkaar vergeleken. Economische evaluaties leveren informatie op die gebruikt kan worden bij de optimale verdeling van de beperkte middelen over gezondheidszorgvoorzieningen op een manier die de gezondheid van de gehele populatie maximaliseert en voorkomt dat ineffectieve of inefficiënte gezondheidszorginterventies worden geïmplementeerd. HTA wordt meestal uitgevoerd wanneer een nieuwe gezondheidzorginterventie geïntroduceerd

kan worden in de klinische praktijk. Echter kan informatie over kosteneffectiviteit ook al eerder in het ontwikkelingsproces van een gezondheidszorginterventie waardevol zijn. Vroege HTA is het gebruik van een economische evaluatie in de vroege ontwikkelingsfase van nieuwe gezondheidszorginterventies. Het doel van vroege HTA is met name om ontwikkelaars te ondersteunen op het moment dat investeringsbesluiten genomen moeten worden, bijvoorbeeld door de optimale doelgroep te bepalen. Daarnaast kunnen patiënten, clinici en besluitvormers in de gezondheidszorg profiteren van tijdige informatie over de (kosten-) effectiviteit van interventies die mogelijk in de toekomst beschikbaar zijn in de klinische praktijk.

Model ontwikkeling

Voordat de vroege HTA van TEHK uitgevoerd kan worden, is een analytisch beslismodel nodig dat informatie over kosten en effecten van hartklepimplantaties vanuit verschillende bronnen kan combineren. De ontwikkeling van dit model is beschreven in het eerste deel van dit proefschrift.

Hoofdstuk 2 beschrijft een van de eerste stappen bij de ontwikkeling van een model: het reviewen van bestaande modellen gericht op gerelateerde problemen. Dit hoofdstuk beschrijft de systematische review van economische modellen voor hartklepimplantaties. Deze studie liet zien dat de methodologische kwaliteit van de huidige gepubliceerde economische modellen voor hartklepimplantaties verbeterd kan worden. Ten eerste door gedetailleerdere beschrijvingen te geven van de bronnen van input parameters en modeleermethoden. Daarnaast door het gebruik van een directe utiliteit beoordeling met een kwaliteit van leven instrument gebaseerd op preferenties in plaats van indirecte utiliteit beoordeling met behulp van de New York Heart Association (NYHA) klasse. Bovendien liet deze review zien dat er ruimte is voor kosteneffectiviteitsanalyses van hartklepimplantaties vanuit een maatschappelijk perspectief, in andere hartklepposities dan de aortaklep, uitgevoerd met behulp van patiëntsimulatiemodellen.

De ontwikkeling van het conceptueel model is beschreven in **Hoofdstuk 3**. Dit conceptuele model diende als de basis voor het analytisch beslismodel dat gebruikt is in dit proefschrift. De ontwikkeling begon met het afbakenen van het vraagstuk en ontwikkelen van een eerste schets van het conceptuele model in een kleine werkgroep. In dit model zijn de, in **Hoofdstuk 2** beschreven, sterke punten en beperkingen van bestaande economische modellen over hartklepimplantaties en de mogelijkheden voor toekomstige modellen meegenomen. Dit model is vervolgens besproken met een Delphi panel met tien experts, waaronder cardio-thoracale chirurgen, cardiologen en een biomedische wetenschapper. Dit resulteerde in een conceptueel model gebaseerd op de inzichten van een multidisciplinaire groep van experts dat de belangrijkste

consequenties van hartklepinterventies weerspiegelt. In het conceptuele model wordt de patiënt gevolgd vanaf het moment van de hartklepimplantatie tot de dood. Patiënten kunnen de interventie overleven of niet (d.w.z. vroege sterfte). Als patiënten de interventie overleven, kunnen zij in leven blijven, overlijden door niet-hartklep-gerelateerde oorzaken (d.w.z. achtergrond en additionele sterfte), of een hartklep-gerelateerde complicatie ervaren. De volgende complicaties zijn geïncludeerd tijdens de gehele simulatie: beroerte, bloeding, falen van de hartklepprothese (structurele klepdegeneratie en non-structurele klepdysfunctie), kleptrombose en endocarditis. Daarnaast zijn de volgende complicaties alleen meegenomen tijdens de eerste dertig dagen na de interventie: hartinfarct, vasculaire complicatie, hartritmestoornissen/ atriumfibrilleren, pacemaker implantatie en (acuut) nierfalen. Patiënten kunnen deze complicaties wel of niet overleven. Als patiënten de complicatie overleven kunnen zij in leven blijven, een volgende complicatie ervaren of overlijden aan niet-hartklep-gerelateerde oorzaken.

Gezondheidsuitkomsten en kosten van bestaande hartklepprotheses
Voordat het analytisch beslismodel gebruikt kan worden voor de vroege HTA van TEHK, moet data verzameld worden voor de input parameters van het model: risico op sterfte en complicaties, gezondheid gerelateerde kwaliteit van leven en maatschappelijke kosten. TEHK worden nog niet gebruikt in de klinische praktijk, daarom moesten aannames gemaakt worden over hun functioneren en kosten. Daarentegen kon het functioneren en de kosten van bestaande hartklepprotheses wel gebaseerd worden op informatie uit de klinische praktijk. Deze resultaten worden beschreven in het tweede deel van dit proefschrift.

Dit proefschrift bevat drie systematische reviews en meta-analyses van klinische uitkomsten na hartklepimplantaties: twee over de uitkomsten na chirurgische aortaklepvervanging en één over de uitkomsten na rechterventrikel uitstroombaan reconstructie (d.w.z. chirurgische pulmonaalklepvervanging).

Hoofdstuk 4 beschrijft de systematische review en meta-analyse van chirurgische aortaklepvervanging met biologische hartkleppen: allografts (menselijke donor) en bioprotheses (dierlijke donor). De resultaten lieten zien dat patiënten die een allograft kregen jonger waren (gemiddelde leeftijd 48.8 vs. 71.8 jaar) en minder vaak gelijktijdig een bypass operatie (d.w.z. coronaire arterie bypass grafting, CABG) ondergingen (11.9% vs. 40.0%) dan patiënten die een bioprothese kregen. Ongeveer 5% van de patiënten overleed binnen 30 dagen na de chirurgische aortaklepvervanging. De meest voorkomende hartklep-gerelateerde complicatie was trombo-embolie na chirurgische aortaklepvervanging met bioprotheses (1.0%/jaar) en structurele klepdegeneratie na

chirurgische aortaklepvervanging met allografts (1.1%/jaar). Re-interventies vonden meestal plaats vanwege structurele klepdegeneratie.

Hoofdstuk 5 is een systematische review en meta-analyse naar de uitkomsten van chirurgische aortaklepvervanging met bioprotheses bij ouderen. De resultaten van de meta-analyse zijn vertaald naar schattingen van de levensverwachting en levenslange risico's op complicaties met behulp van het analytisch beslismodel. Zoals verwacht waren het risico op vroege sterfte (5.4 vs. 5.0%) en de 'linearized occurrence rates' van de meeste late complicaties hoger (non-structurele klepdysfunctie 0.5 vs. 0.2 %/jaar; trombo-embolie 1.8 vs. 1.1%/jaar; bloeding 0.8 vs. 0.4%/jaar; endocarditis 0.6 vs. 0.4%/jaar), terwijl de linearized occurrence rates van structurele klepdegeneratie (0.4 vs. 0.5%/jaar) en re-interventie (0.6 vs. 0.7%/jaar) lager waren na chirurgische aortaklepvervanging met bioprotheses bij ouderen dan bij patiënten van alle leeftijden **(Hoofdstuk 4)**. Het relatief weinig voorkomen van structurele klepdegeneratie (levenslang risico 7.2% bij 75-jarigen en 2.8% bij 85-jarigen) bevestigt de aanbeveling in klinische richtlijnen om bioprotheses in plaats van mechanische protheses te gebruiken bij ouderen die een aortaklepvervanging nodig hebben. De levensverwachting van patiënten na chirurgische aortaklepvervanging met bioprotheses was vergelijkbaar met de algemene bevolking met vergelijkbare leeftijds- en geslachtsverdeling. Dit wordt waarschijnlijk veroorzaakt door de zorgvuldige selectie van relatief gezonde ouderen om chirurgische aortaklepvervanging te ondergaan, terwijl kwetsbare ouderen niet in aanmerking komen voor de operatie.

Hoofdstuk 9 bevat de systematische review en meta-analyse van rechterventrikel uitstroombaan reconstructie bij kinderen. De meeste patiënten jonger dan twee jaar werden geopereerd voor truncus arteriosus communis (TAC; 66.5%) gevolgd door tetralogie van Fallot (TOF, 14.6%). De pulmonaalklep werd meestal vervangen door biologische protheses (allografts 61.2% of bioprotheses 38.7%) in plaats van mechanische protheses, omdat het risico op kleptrombose bij mechanische protheses in de pulmonaalkleppositie hoger is dan in de aortakleppositie. Daarentegen werden de meeste patiënten ouder dan twee jaar geopereerd voor TOF (42.5%) gevolgd door TAC (13.1%) en werd de pulmonaalklep vervangen door allografts (42.1%), bioprotheses (40.3%), of synthetisch polytetrafluorethylene (PTFE; 17.1%) prostheses. Vroege sterfte kwam vaker voor bij kinderen jonger dan twee jaar (11%) dan bij oudere kinderen (4.7%). Daarnaast was het risico op re-interventie aanzienlijk hoger bij kinderen jonger dan twee jaar (vijf jaar vrijheid van re-interventie 46.1% bij leeftijd ≤2 jaar vs. 81.1% leeftijd >2 jaar). Daarentegen werden andere hartklep-gerelateerde complicaties niet gerapporteerd bij kinderen jonger dan twee jaar.

Hartklepimplantaties hebben meer gevolgen dan alleen het risico op sterfte en complicaties. Deze impact is onderzocht in **Hoofdstuk 6**, waarin de resultaten worden gepresenteerd van een vragenlijst ingevuld door patiënten over gezondheid gerelateerde kwaliteit van leven, gebruik van mantelzorg en productiviteit van patiënten na chirurgische aortaklepvervanging (n=633), transkatheter aortaklepimplantatie (TAVI; n=257) en rechterventrikel uitstroombaan reconstructie (n=26). De resultaten lieten zien dat patiënten na aorta- en pulmonaalklepimplantaties relatief milde beperkingen ervaarden in hun dagelijks leven in vergelijking met de algemene bevolking. Gemiddeld hadden patiënten na chirurgische en transkatheter aortaklepvervanging een lagere gezondheid gerelateerde kwaliteit van leven dan de algemene bevolking, terwijl patiënten na rechterventrikel uitstroombaan reconstructie een iets betere gezondheid gerelateerde kwaliteit van leven hadden dan de algemene bevolking. Specifiek hadden patiënten een slechtere gezondheid gerelateerde kwaliteit van leven op fysieke gezondheidsdomeinen dan de algemene bevolking, terwijl hun scores vergelijkbaar of iets hoger waren op mentale gezondheidsdomeinen. Daarnaast gebruikten patiënten vaker mantelzorg, maar de hoeveelheid mantelzorg per patiënt was lager dan bij gebruikers van mantelzorg in de algemene bevolking. Ten slotte was de arbeidsparticipatie van patiënten vergelijkbaar met de algemene bevolking. De grote meerderheid van de ouderen na chirurgische of transkatheter aortaklepvervanging hadden geen betaald werk, maar meer dan een derde van deze patiënten rapporteerde onbetaalde werkzaamheden (bv. vrijwilligerswerk of oppassen).

Hoofdstuk 7 beschrijft de retrospectieve analyses van de declaraties bij zorgverzekeraars van alle Nederlandse patiënten die een hartklepimplantatie hebben ondergaan tussen 2010 en 2013 (n=18,903) en van een controlegroep met personen uit de algemene bevolking (n=188,925). In deze studie zijn kosten van hartklepimplantaties, behandeling van complicaties en gezondheidszorggebruik binnen en buiten het ziekenhuis in de jaren na de hartklepimplantatie bepaald voor vier leeftijdsgroepen. De gemiddelde kosten van de hartklepimplantaties die behandeld worden in dit proefschrift zijn €25,165 voor chirurgische aortaklepvervanging en €32,209 voor TAVI bij oudere patiënten en €21,800 voor rechterventrikel uitstroombaan reconstructie bij kinderen. Re-interventies hadden de hoogste gezondheidszorgkosten (vergelijkbaar met de kosten van de initiële interventie). Daarna volgen de kosten van ziekenhuisopname voor antibioticabehandeling van endocarditis (gemiddeld €8,069 bij kinderen na rechterventrikel uitstroombaan reconstructie en €8,923 bij ouderen na aortaklepvervanging). Trombolyse bij hartkleptrombose had de laagste kosten van alle hartklep-gerelateerde complicaties (€5,824). 'Multilevel generalized linear models' lieten zien dat hogere leeftijd, vrouwelijk geslacht, comorbiditeiten en lage sociaaleconomische status en complicaties gepaard gingen met verhoogde

jaarlijkse gezondheidszorgkosten bij patiënten na een hartklepimplantatie. De totale gezondheidszorgkosten van patiënten na een hartklepimplantatie werden vergeleken met de totale gezondheidszorgkosten van de controlegroep. Deze kosten waren hoger bij patiënten dan in de controlegroep, met name in het jaar van de hartklepimplantatie (leeftijd 0-18 jaar €11,766 vs. €796, 19-60 jaar €15,060 vs. €2,944, 61-70 jaar €16,104 vs. €4,612, en boven de 70 jaar €18,255 vs. €9,236). Maar ook in de opvolgende jaren waren de gezondheidszorgkosten van patiënten hoger dan van personen in de controlegroep, met name bij kinderen (jaar 2 €5,495 vs. €802; jaar 3 €5,015 vs. €786). Bij ouderen waren de kosten van verpleeghuiszorg lager bij patiënten na chirurgische aortaklepvervanging dan in de controlegroep (€866 in jaar 1, €1,763 in jaar 2 en €1,990 in jaar 3 na de hartklepimplantatie versus €2,761 per jaar in de controlegroep), als gevolg van de selectie van relatief gezonde ouderen (die daarom niet in verpleeghuizen wonen) om chirurgische aortaklepvervanging te ondergaan.

Vroege Health Technology Assessment van TEHK

Het derde deel van dit proefschrift beschrijft de vroege HTA van TEHK met gebruik van het analytisch beslismodel en de input parameters beschreven in de vorige delen van dit proefschrift. Dit proefschrift beschrijft het gebruik van TEHK in de aorta- en pulmonaalkleppositie. **Hoofdstuk 8** richt zich op aortaklepvervangingen bij ouderen, omdat de prevalentie van aortaklepafwijkingen het hoogste is in deze leeftijdsgroep vanwege het slijten van de eigen hartklep. **Hoofdstuk 9** richt zich op pulmonaalklepvervangingen bij kinderen, omdat pulmonaalklepafwijkingen meestal veroorzaakt worden door aangeboren hartafwijkingen.

In beide studies zijn de kosteneffectiviteit, budget impact en 'headroom' van TEHK ten opzichte van bestaande hartklepprotheses bepaald door verschillende scenario's voor het functioneren van TEHK te modelleren. Het functioneren van TEHK was verdeeld in drie componenten: duurzaamheid, trombogeniciteit en infectie resistentie. In beide patiëntengroepen had verbetering in duurzaamheid de meeste invloed op 'quality-adjusted life years' (QALY) winst en kostenbesparingen (variërend van 0.049-0.152 QALY en €118-€634 per chirurgische aortaklepvervanging patiënt, 0.023-0.074 QALY en €156-€586 per TAVI patiënt, en 0.031-0.083 QALY en €5,691-€20,568 per rechterventrikel uitstroombaan reconstructie patiënt voor kleine verbeteringen in duurzaamheid tot optimale duurzaamheid van TEHK).

Bovendien was de headroom (d.w.z. de maximale verhoging van de prijs van TEHK t.o.v. de prijs van bestaande hartklepprothesen) groot genoeg om TEHK economisch levensvatbaar te maken. De headroom varieerde van €38 per chirurgische tissue-engineered aortaklep, €35 per transkatheter tissue-engineered aortaklep, en €12 per chirurgische tissue-engineered pulmonaalklep als TEHK slechts tot een

kleine verbetering in trombogeniciteit zouden leiden tot €6,323 per chirurgische tissue-engineered aortaklep, €4,734 per transkatheter tissue-engineered aortaklep, en €23,041 per chirurgische tissue-engineered pulmonaalklep als patiënten met TEHK geen enkele hartklep-gerelateerde complicaties zouden ervaren.

De grootste individuele winst kan worden behaald bij kinderen die pulmonaalklepvervanging (d.w.z. rechterventrikel uitstroombaan reconstructie) met TEHK ondergaan, omdat de kans op re-interventie met bestaande hartklepprotheses hoog is en gepaard gaat met hoge kosten. Echter is het aantal kinderen dat rechterventrikel uitstroombaan reconstructie ondergaat in Nederland klein (85 per jaar). Als we uitgaan van een 'verbeterde prestatie' van TEHK (-50% hartklep-gerelateerde complicaties) dan variëren de nationale kostenbesparingen in de komende 10 jaar van €1.9 miljoen, wanneer 25% van de rechterventrikel uitstroombaan reconstructies uitgevoerd wordt met TEHK, tot €7.5 miljoen, wanneer alle rechterventrikel uitstroombaan reconstructies uitgevoerd wordt met TEHK in plaats van bestaande hartklepprotheses. De individuele winsten die behaald kunnen worden met het gebruik van TEHK bij ouderen patiënten die (chirurgische of transkatheter) aortaklepimplantatie ondergaan waren lager, omdat het risico op re-interventie met de bestaande bioprotheses laag was bij deze patiënten. Echter, de relatief lage individuele QALY winsten en kostenbesparingen met TEHK in ouderen patiënten kunnen resulteren in grote nationale kostenbesparingen vanwege de relatief grote omvang van deze patiëntenpopulatie (1,931 chirurgische aortaklepvervangingen/jaar; 809-3,745 TAVI/jaar). De nationale kostenbesparingen in de komende tien jaar met TEHK met 'verbeterde prestatie' (-50% hartklep gerelateerde complicaties) varieerde tussen €2.8 miljoen (SAVR) en €3.2 miljoen (TAVI) als bij 25% van de hartklepimplantaties TEHK gebruikt worden tot €11.2 miljoen (chirurgische aortaklepvervanging) en €12.8 miljoen (TAVI) als bij alle hartklepimplantaties TEHK gebruikt worden in plaats van bioprotheses.

Discussie en conclusie

In **Hoofdstuk 10** wordt besproken hoe besluitvorming bij structurele hartafwijkingen geoptimaliseerd kan worden vanuit drie perspectieven. Vanuit een klinisch perspectief kan besluitvorming geoptimaliseerd worden door de ontwikkeling en gebruik van nieuwe prognostische modellen die in staat zijn om tegelijkertijd verschillende longitudinale data, verzameld tijdens de follow-up van patiënten, te combineren met patiënten uitkomsten. Vanuit een patiënten perspectief kan gedeelde besluitvorming bevorderd worden door de implementatie van informatieportalen en keuzehulpen die patiënten in staat stellen om de voor- en nadelen van behandelingen tegen elkaar af te wegen. Vanuit een maatschappelijk perspectief zou het gebruik van informatie over kosteneffectiviteit door beleidsmakers kunnen zorgen voor een optimale verdeling

van de beperkte middelen over gezondheidszorgvoorzieningen op een manier die de gezondheid van de gehele populatie maximaliseert en die voorkomt dat ineffectieve of inefficiënte gezondheidszorginterventies worden geïmplementeerd.

Ten slotte worden in **Hoofdstuk 11** de drie onderdelen van dit proefschrift, de implicaties van de resultaten voor verschillende belanghebbenden en de aanbevelingen voor toekomstig onderzoek besproken. Ten eerste informeert dit proefschrift biomedische bedrijven die TEHK ontwikkelen over de minimale prestatie-eisen en de maximale additionele kosten van TEHK in verschillende doelgroepen. Dit kan hen helpen bij het stellen van prioriteiten in vervolgonderzoeken. Dit proefschrift laat zien dat ontwikkelaars van TEHK zich met name moeten richten op het verbeteren van de duurzaamheid van TEHK in vergelijking met bestaande hartklepprotheses, omdat dit de grootste invloed had op QALY winsten en kostenbesparingen. Echter moet worden opgemerkt dat de potentiele verbetering in trombogeniciteit van TEHK ten opzichte van bestaande hartklepprotheses naar verwachting voor grotere winsten kan leiden in andere patiëntenpopulaties dan onderzocht in dit proefschrift (d.w.z. bij jongvolwassenen of patiënten van middelbare leeftijd die in aanmerking komen voor mechanische hartklepprotheses). Verder was de headroom groot genoeg om TEHK economisch levensvatbaar te maken. Ten tweede voorziet dit proefschrift patiënten en clinici van de eerste schattingen van de potentiele verbeteringen in klinische uitkomsten met TEHK. Mogelijk resulteert dit in een snellere implementatie van TEHK in de klinische praktijk. Ten slotte informeert dit proefschrift financierders van gezondheidszorg over de mogelijke toetreding van TEHK in de markt, de veelbelovende potentiele kosteneffectiviteit van TEHK en de grote verwachte kostenbesparingen voor het nationale gezondheidszorgbudget, wat mogelijk leidt tot tijdige besluiten over vergoeding van TEHK.

DANKWOORD

Na afloop van de verdediging van mijn masterscriptie vroeg professor Maureen Rutten-van Mölken, meelezer van mijn masterscriptie, mij naar mijn toekomstplannen en of ik al had overwogen promotieonderzoek te gaan doen. Zo ja, dan had zij wel een aantal opties voor me. Tot op dat moment had ik er niet bij stil gestaan dat promoveren tot de mogelijkheden behoorde. Maar toen ik er wat langer over nagedacht had, besefte ik dat dit goed bij mij zou kunnen passen. Bovendien sprak een van de onderwerpen die Maureen beschikbaar had, de vroege HTA van tissue-engineered hartkleppen, mij enorm aan. Ik heb affiniteit met dit onderwerp, omdat mijn nicht Lisanne geboren is met een hartklepafwijking en al meerdere hartklepvervangingen heeft ondergaan. In april 2014 werd ik uitgenodigd voor een sollicitatiegesprek met professor Hanneke Takkenberg in het Erasmus MC, die mij vervolgens aangenomen heeft voor deze promotieplek. Ruim vier jaar later is dit het eindresultaat.

Dit proefschrift had ik niet kunnen voltooien zonder de begeleiding en steun van velen om me heen. Voor hun bijdrage aan de totstandkoming van dit proefschrift wil ik een aantal personen specifiek bedanken.

Allereerst wil ik mijn promotoren bedanken, professor Takkenberg en professor Rutten-van Mölken. Beste Hanneke, beste Maureen, ik ben trots dat ik jullie mijn promotoren mag noemen. Met jullie verschillende expertisen en persoonlijkheden vullen jullie elkaar goed aan. Na onze overleggen was ik altijd weer extra gemotiveerd en vol vertrouwen om mijn promotieonderzoek voort te zetten.

Maureen, allereerst bedankt voor je vertrouwen en de kans die je mij gegeven hebt door mij een promotieplek aan te bieden. Daarnaast wil ik je bedanken voor de fijne begeleiding de afgelopen jaren. Jouw scherpe blik en zorgvuldige en opbouwende feedback, waarbij je niet alleen aandacht had voor wat beter kon maar waarbij je ook de positieve punten benoemde, heb ik altijd zeer gewaardeerd. Hierdoor kreeg ik het gevoel op de goede weg te zijn en gaf je mij richting om mijn promotieonderzoek naar een hoger plan te tillen. Ik ben blij dat we onze samenwerking nu in nieuwe projecten kunnen voortzetten.

Hanneke, bedankt dat je mij wegwijs hebt gemaakt in de wereld van de thoraxchirurgie en voor je altijd enthousiasmerende begeleiding. Ik heb veel van je geleerd, niet alleen door je kennis over hartkleppen en epidemiologie, maar ook door je pakkende schrijfstijl en politieke vaardigheden. Ondanks je drukke agenda kon ik altijd bij je binnen lopen wanneer ik vragen had en had je ook aandacht voor mijn persoonlijke ontwikkeling. Ik heb veel bewondering voor de manier waarop jij je inzet om diversiteit

en inclusie in de wetenschap te bevorderen. Bedankt voor alles en ik hoop dat onze wegen in de wetenschap zich ook in de toekomst nog zullen kruisen.

Graag wil ik dr. Maiwenn Al, professor dr. mr. Bas de Mol en professor dr. Simon Hoerstrup hartelijk danken voor het plaatsnemen in de kleine commissie en voor het lezen en beoordelen van mijn proefschrift. Tevens wil ik professor dr. Manuele Joore, professor dr. Werner Brouwer en dr. Maarten Witsenburg bedanken voor het zitting nemen in mijn grote commissie.

Door de begeleiding van twee promotoren werkzaam in verschillende instituten, heb ik mijn tijd verdeeld over het Erasmus MC en het instituut Beleid & Management voor de Gezondheidszorg, of tegenwoordig Erasmus School of Health Policy & Management (ESHPM). Op beide werkplekken heb ik het goed getroffen met mijn collega's. Hanneke vertelde mij tijdens mijn sollicitatiegesprek al dat er op de afdeling Thoraxchirurgie een gezellige groep PhD studenten was. Niets bleek minder waar. Eerst kreeg ik een werkplek in kamer BD-575, waar ik meestal het rijk voor mij alleen had. Maar toen na een jaar een plek vrij kwam in de naastliggende kamer BD-577, twijfelde ik geen moment en verhuisde ik naar de buren. Deze kamer heeft in de loop der jaren verschillende formaties gekend. Beginnend met Nelleke, Sahar, Jonathan en Gerdien, gevolgd door Isabel, Kevin, Daan en Arjen. In elke formatie hebben we in deze kamer lief en leed gedeeld, gebrainstormd en elkaar geholpen met het opstellen van moeilijke e-mails, ontwerpen van posters voor congressen en het uitvoeren van statistische analyses. Lieve BD-577-kamergenootjes en andere mede-promovendi, bedankt voor jullie hulp als ik weer eens een medische vraag had, maar vooral bedankt voor de gezelligheid! Ik heb hele leuke herinneringen aan onze gezamenlijke lunches, Thanksgiving diners en Heart Valve Society congressen. Hierbij wil ik in het bijzonder Jonathan bedanken voor de plezierige samenwerking tijdens het uitvoeren van onze systematische reviews, het begeleiden van studenten, maar vooral voor al die uren dat we samen hebben gepiekerd om de kinderziektes van ons patiëntensimulatiemodel te verhelpen. Bedankt voor al je hulp en steun en wat fijn dat je ook tijdens mijn verdediging naast mij wilt staan als mijn paranimf! Verder wil ik alle thoraxchirurgen, datamanagers, onderzoekscoördinatoren en de medewerkers van het secretariaat van de afdeling Thoraxchirurgie bedanken voor hun hulp bij mijn promotieonderzoek.

Op donderdag en vrijdag werkte ik meestal bij ESHPM en ook hier heb ik het altijd erg naar mijn zin gehad. Het was fijn om een paar dagen per week bij mijn oude vertrouwde faculteit aan het werk te zijn. Bij vragen of problemen was er altijd wel iemand bereid om te helpen. Ook bij ESPHM heb ik goede herinneringen aan de lunches op J7 en de congresbezoeken naar ISPOR en EuHEA. Bovendien was het heel fijn om mijn goede vriendinnen Brenda en Jeanine in de buurt te hebben.

Daarnaast heb ik in de flexruimte op J7 Marscha en Frédérique leren kennen, met als gevolg vele gezellig etentjes bij jullie thuis. Bedankt daarvoor en voor jullie interesse in mijn promotieonderzoek.

Mijn promotieonderzoek was onderdeel van het 1Valve consortium van Cardiovasculair Onderzoek Nederland (CVON), een samenwerking tussen TU Eindhoven, AMC, UMC Utrecht en Erasmus MC. Binnen dit consortium was ik een beetje een vreemde eend in de bijt, als gezondheidseconoom tussen alle biomedische wetenschappers en artsen. Ik moet toegeven dat ik niet alle presentaties over 'tissue homeostasis', 'sheer stress' en 'electrospun polymers' helemaal heb kunnen volgen, maar ik vond het altijd heel inspirerend om te zien waar jullie mee bezig waren. Bedankt voor jullie input en interesse in mijn onderzoek.

Professor Carlijn Bouten en Hanneke wil ik bedanken voor de kans die zij Marcelle en mij hebben gegeven om onze organisatievaardigheden verder te ontwikkelen door het organiseren van de eerste 'International Conference of Tissue Engineered Heart Valves' (ICTEHV). Marcelle, bedankt voor de leuke samenwerking bij het organiseren van de Hartkleppendag en ICTEHV. Nog steeds ben ik supertrots dat wij samen met de overige bestuursleden, Kevin, Pepijn, Jesper, Mostafa en Dimitri, zo'n succesvolle eerste ICTEHV hebben neergezet. Bedankt jongens! Hierbij wil ik Kevin nog extra bedanken, die mijn uitnodiging om deel te nemen in het bestuur direct met beide handen aangreep en een groot deel van het werk op zich heeft genomen. Zonder jou hadden we het niet kunnen doen!

Daarnaast wil ik alle co-auteurs van de studies in dit proefschrift bedanken. Een aantal co-auteurs wil ik hierbij in het bijzonder bedanken. Professor Bogers en dr. Bekkers vanwege hun klinische input bij een groot deel van mijn publicaties. Dr. Bekkers wil ik daarnaast bedanken voor zijn hulp bij het contact leggen met perifere ziekenhuizen voor het verzamelen van patiëntengegevens. Dr. van der Kley voor zijn bereidheid samen te werken bij het uitzetten van vragenlijsten onder TAVI patiënten in het Leiden Universitair Medisch Centrum. Bianca, Milad, Gjorgi en Anahita, voor hun hulp bij het verzamelen van patiëntengegevens of de data-extractie voor systematische reviews. Niels Hoeksema en Judith van Erkelens van Vektis voor hun hulp bij het uitvoeren van de kostenanalyse van declaraties bij zorgverzekeraars en voor hun gastvrijheid in Zeist. Lucas voor zijn hulp bij de statistische analyses van de Vektis data. Isaac voor zijn onmisbare hulp bij een aantal essentiële elementen van het patiëntensimulatiemodel.

Maureen, Carin en Matthijs wil ik bedanken voor de kans die ze mij hebben gegeven om mijn carrière voor te zetten bij iMTA. Daarnaast bedank ik graag al mijn collega's bij iMTA en ESHPM voor hun warme ontvangst en de fijne samenwerking die wij nu hebben.

Niet alleen mijn collega's, maar ook mijn familie en vrienden zijn heel belangrijk voor mij geweest tijdens het schrijven van dit proefschrift. Ik wil jullie allen bedanken voor jullie steun en belangstelling in mijn proefschrift. Hierbij wil ik een aantal mensen in het bijzonder noemen.

Lieve Pauline, als zo lang als ik mij kan herinneren zijn wij beste vriendinnen en ik kan mij ook niet voorstellen dat dit gaat veranderen. Je hebt alle pieken en dalen tijdens het schrijven van dit proefschrift meegemaakt en stond altijd voor mij klaar. Daarom vind ik het heel bijzonder dat jij de tekeningen voor de voorkant van dit proefschrift hebt gemaakt. Ik vond het erg leuk om samen met jou te brainstormen over de tekeningen en ik ben heel blij met het resultaat. Dat heeft dit proefschrift een extra persoonlijk tintje gegeven.

Lieve Brenda, ik zou mij geen promotietraject zonder jou kunnen voorstellen. Het was en is heel fijn om een goede vriendin als collega te hebben. Bedankt dat jij aan mijn zijde wilt staan als paranimf tijdens mijn promotie!

Lieve Marjolein, Ruth en Jeanine, ik ben blij dat wij ook na onze studie contact zijn blijven houden en hoop dat we dat nog lang volhouden. Het was fijn om met jullie ook over de inhoudelijke aspecten van mijn promotieonderzoek te kunnen praten. Maar vooral bedankt voor de vele gezellige etentjes, borrels en festivalbezoeken de afgelopen jaren!

Lieve Femke, Susanna en Paulien, de middelbare school ligt inmiddels al lang achter ons en we zijn allemaal onze eigen weg gegaan, maar gelukkig lukt het zo nu en dan om onze drukke agenda's op elkaar af te stemmen. Altijd als we elkaar dan weer zien, voelt het heel vertrouwd. Bedankt voor jullie vriendschap en belangstelling in mijn promotieonderzoek!

Lieve Lisanne, lieve nicht, door jou kon ik verder kijken dan de cijfertjes op mijn beeldscherm en had ik een beeld van de patiënten waarvoor we dit onderzoek doen. Ik heb veel bewondering voor hoe je in het leven staat. Jouw hartafwijking heeft je nooit in de weg gestaan om je doelen te bereiken. Bedankt voor je interesse in mijn promotieonderzoek, je gezelligheid, steun en de goede gesprekken die we hopelijk nog vaak zullen hebben.

Lieve papa, mama en Eveline, samen vormen wij een hecht gezin. Jullie stonden en staan altijd voor mij klaar en dat betekent heel veel voor me. Ik wil jullie bedanken voor jullie luisterend oor, wijze raad en onvoorwaardelijke steun en liefde. Ik koester de bijzondere band die ik met jullie heb.

Lieve mama, bedankt voor al je goede zorgen, zeker in de laatste periode van mijn promotietraject, waardoor ik mij kon focussen op het afronden van mijn proefschrift. Jij leerde mij om altijd eerst hetgeen te doen waar ik tegenop zie of wat af moet, om vervolgens optimaal te kunnen genieten van mijn vrije tijd. De zelfdiscipline die ervoor nodig is om dit ook daadwerkelijk te doen heb ik van jou. De vrije tijd die daarop volgt, spendeer ik graag samen met jou op de bank met een kopje thee en een nieuwe aflevering van een serie die we samen volgen.

Lieve papa, jij hebt mij en Eveline altijd uitgedaagd om het meeste uit onszelf te halen. Hoewel ik je adviezen op het moment zelf misschien niet altijd kan waarderen, moet ik toegeven dat je achteraf (meestal) gelijk hebt. Bedankt dat je er altijd voor mij bent als ik je hulp of advies nodig heb en ik hoop dat we nog lang samen zullen hardlopen.

Lieve Eef, ik zou mij geen betere zus kunnen wensen. Ondanks dat je mijn kleine zusje bent, geef je mij regelmatig wijze raad. Bedankt dat ik altijd alles met je kan bespreken en dat ik altijd bij je terecht kan. Lieve Jelte, je bent inmiddels niet meer weg te denken uit ons gezin en ik ben erg blij met onze goede band. Bovendien vind ik het leuk dat wij nu onze PhD-ervaringen met elkaar kunnen delen. Het klinkt misschien gek, maar ik wil ook onze lieve hond Charlie bedanken, omdat hij mij altijd vrolijk maakt!

Lieve opa en oma's, bedankt voor jullie belangstelling in mijn proefschrift, waarbij jullie altijd lieten merken dat jullie trots op mij zijn. Dat doet me heel goed en daarom draag ik dit proefschrift op aan jullie (ook aan de opa die ik helaas nooit gekend heb, maar van wie ik met trots zijn naam draag). Ik bewonder de positieve manier waarop jullie in het leven staan. Ik voel mij bevoorrecht dat ik jullie nog steeds in mijn leven heb en ik hoop dat ik ook de verdediging van dit proefschrift met jullie mag delen.

ABOUT THE AUTHOR

Simone Huygens was born in Zwijndrecht on September 11th 1991. In 2009 she started the bachelor program Health Policy & Management at the Erasmus University Rotterdam (2009-2012). In 2013, she obtained her master's degree in Health Economics, Policy & Law from the Erasmus University Rotterdam. During her master's, she specialized in Health Technology Assessment. After graduation, Simone started as a PhD candidate at the department of Cardio-Thoracic Surgery of the Erasmus Medical Centre Rotterdam under supervision of prof. dr. J.J.M. Takkenberg and prof. dr. M.P.M.H. Rutten-van Mölken, which resulted in this thesis. Her PhD project was part of the Netherlands Cardio Vascular Research Initiative (Cardiovasculair Onderzoek Nederland; CVON) consortium called 1Valve and mainly focused on the early Health Technology Assessment of tissue-engineered heart valves. Besides this research, Simone was treasurer of the organizing committee of the first International Conference of Tissue-Engineered Heart Valves (ICTEHV) which took place on the 18th of May 2018 at the EYE Filmmuseum in Amsterdam. After completing her PhD research, Simone continued her career as a researcher at the Institute for Medical Technology Assessment (iMTA) of the Erasmus University of Rotterdam.

PHD PORTFOLIO

Name PhD student:	Simone Huygens
Erasmus MC department:	Cardio-Thoracic Surgery
Research school:	Cardiovascular Research School (COEUR)
PhD period:	May 2014-September 2018
Title thesis:	Early Health Technology Assessment of Tissue-Engineered Heart Valves
Promotors:	Prof. dr. J.J.M. Takkenberg Prof. dr. M.P.M.H. Rutten-van Mölken
Date of defense thesis:	February 20, 2019

Academic education

2009-2012	Bachelor of Science (BSc) in Health Policy and Management, Erasmus University Rotterdam, the Netherlands
2012-2013	Master of Science (MSc) in Health Economics, Policy and Law, Erasmus University Rotterdam, the Netherlands

PhD training (36 ECTS)

In-depth courses (16 ECTS)

2014	Modeling Approaches for Health Technology Assessment: A Practical Hands-on Workshop, *University for Health Sciences Medical Informatics and Technology*
2014	Early Health Technology Assessment, *Panaxea and the University of Twente*
2014	How to use EndNote? *Medical Library Erasmus University Medical Centre*
2014	Systematic Literature Retrieval in Pubmed and other databases, *Medical Library Erasmus University Medical Centre*
2014	Introduction to database analysis of observational studies of treatment effects, *ISPOR*
2014	Meta-analysis & Systematic Literature Review, *ISPOR*
2014	Discrete Event Simulation for Economic Analyses, *ISPOR*
2014	Cardiovascular epidemiology, *COEUR*
2015	Basic course on R, *Erasmus Postgraduate School Molecular Medicine*
2015	Patient Oriented Research: design, conduct, analysis and clinical implications, *Centre for Patient Oriented Research Erasmus University Medical Centre*
2015	Conceptual Foundation of Epidemiologic Study Design, *Netherlands Institute of Health Sciences*

2015	Survival analysis, *Netherlands Institute of Health Sciences*
2015	Practice of Epidemiologic Analysis, *Netherlands Institute of Health Sciences*
2016	Scientific integrity, *Erasmus University Medical Centre*
2016	Advanced Analysis of Prognosis Studies, *Netherlands Institute of Health Sciences*
2016	Decision analytic modeling for economic evaluation - Advanced, *Centre for Health Economics, University of York*
2016	Indirect medical costs, *institute for Medical Technology Assessment*
2016	Budget impact analysis, *ISPOR*
2016	Biomedical English Writing and Communication, *Erasmus University Medical Centre*
2017	Patient level modeling in R, *institute for Medical Technology Assessment*

Teaching (5 ECTS)

2014 & 2015	Supervision 2nd year medical students in writing a systematic review, *Erasmus University Medical Centre*
2015 & 2017	Supervision 3rd year medical students in writing a systematic review as part of the minor 'Congenital heart diseases', *Erasmus University Medical Centre*
2016	Supervision research project of a NIHES research master student, *Erasmus University Medical Centre*
2017	Lecture 'Health Technology Assessment' Bachelor students, *Delft University of Technology*
2017	Presentation during the course 'Congenital Heart Disease', *COEUR*
2017	Tutor working groups 'Advanced research methods', *Erasmus School of Health Policy & Management*

Conferences (10 ECTS)

2014	International Society of Pharmacoeconomics and Outcomes Research 17th Annual European Congress in Amsterdam
2015	International Society of Pharmacoeconomics and Outcomes Research 18th Annual European Congress in Milan (poster presentation)
2016	Heart Valve Society Meeting 2nd Annual Meeting in New York (moderated poster presentation)
2016	International Society of Pharmacoeconomics and Outcomes Research 19th Annual European Congress in Vienna (poster presentation)
2017	Heart Valve Society 3rd Annual Meeting in Monaco (oral presentation)

2017	Lowlands Health Economic Study Group (lolaHESG) conference in Rotterdam
2018	Heart Valve Society 4th Annual Meeting in New York (moderated poster presentation)
2018	International Conference of Tissue Engineered Heart Valves in Amsterdam (member of the organisation committee)
2018	Society of Medical Decision Making in Leiden (poster presentation)
2018	European Health Economics Association in Maastricht (poster presentation)

Other meetings and symposia (5 ECTS)

2014-2018	Journal Club meetings department of Cardio-Thoracic Surgery, *Erasmus University Medical Centre*
2016-2018	HTA lunch seminars, *Erasmus School of Health Policy & Management*
2014 & 2016	COEUR PhD day, *Erasmus University Medical Centre*
2014 & 2015	Erasmus MC PhD day, *Erasmus University Medical Centre*
2014 & 2016	Puls, *Dutch Heart Foundation*
2016	Heart valve day, *patient foundation 'Hart & Vaatgroep'* and others.
2016	Launch new Dutch Guidelines for Economic Evaluation in Healthcare, *Zorginstituut Nederland*
2017	'When is it too expensive?' symposium, *institute for Medical Technology Assessment*
2017	'Right to health care' symposium, *Vereniging voor Gezondheidseconomie*

Awards and grants

2015	1Valve Young Talent Program Acceleration and Career Development Grant
2016	1Valve Talent Program Acceleration and Career Development Grant
2018	Best poster presentation at the Heart Valve Society 4th Annual Meeting in New York

LIST OF PUBLICATIONS

Simone A. Huygens, Maureen P.M.H. Rutten-van Mölken, Anahita Noruzi, Jonathan R.G. Etnel, Isaac Corro Ramos, Carlijn V.C. Bouten, Jolanda Kluin, Johanna J.M. Takkenberg. What is the potential of tissue-engineered pulmonary valves in children? An Early Health Technology Assessment study. *Ann Thorac Surg*. In press.

Simone A. Huygens, Jonathan R.G. Etnel, Milad Hanif, Jos A. Bekkers, Ad J.J.C. Bogers, Maureen P.M.H. Rutten-van Mölken, Johanna J.M. Takkenberg. Bioprosthetic aortic valve replacement in the elderly: meta-analysis & microsimulation. *JTCVS*. In press.

Simone A. Huygens, Frank van der Kley, Jos A. Bekkers, Ad J.J.C. Bogers, Johanna J.M. Takkenberg, Maureen P.M.H. Rutten-van Mölken. Beyond the clinical impact of heart valve implantations: Health-related quality of life, use of informal care, and productivity after a heart valve implantation *EJCTS*. In press.

Jonathan R.G. Etnel*, Pepijn Grashuis*, **Simone A. Huygens**, B. Pekbay, Grigorios Papageorgiou, Willem A. Helbing, Jolien W. Roos Hesselink, Ad J.J.C. Bogers, M. Mostafa Mokhles, Johanna J.M. Takkenberg. The Ross procedure: an updated systematic review, meta-analysis and microsimulation. *Circulation: Cardiovascular Quality & Outcomes*. In press.

Simone A. Huygens, Lucas M.A. Goossens, Judith A. van Erkelens, Johanna J.M. Takkenberg, Maureen P.M.H. Rutten-van Mölken. How much does a heart valve implantation cost and what are the health care costs afterwards? *Open Heart*. 2018;5:e000672

Mostafa M. Mokhles, **Simone A. Huygens**, Johanna J.M. Takkenberg. Is there a risk in avoiding risk? *Structural Heart*. 2018;2(1):30-36

Simone A. Huygens, Johanna J.M. Takkenberg, Maureen P.M.H. Rutten-van Mölken. Systematic review of model-based economic evaluations of heart valve implantations. E*ur J Health Econ*. 2018;19:241-255.

Benjamin P. Geisler, **Simone A. Huygens**, Michael J. Reardon, Nicolas Van Mieghem, Arie Pieter Kappetein, Ruben L. J. Osnabrugge & Jan B. Pietzsch. Cost-effectiveness and Projected Survival of Self-expanding Transcatheter versus Surgical Aortic Valve Replacement for High Risk Patients in a European Setting. A Dutch Analysis Based on the CoreValve High-Risk Trial. *Structural Heart*. 2017.

Simone A. Huygens, Maureen P.M.H. Rutten-van Mölken, Jos A. Bekkers, Ad J.J.C Bogers, Carlijn V.C. Bouten, Steven A.J. Chamuleau, Peter P.T. de Jaegere, Arie Pieter Kappetein, Jolanda Kluin, Nicolas M.D.A. van Mieghem, Michel I.M. Versteegh, Maarten Witsenburg, Johanna J.M. Takkenberg. Conceptual model for early health technology assessment of current and novel heart valve interventions. *Open Heart*. 2016;3:e000500.

Simone A. Huygens, Mostafa M. Mokhles, Milad Hanif, Jos A. Bekkers, Ad J.J.C. Bogers, Maureen P.M.H. Rutten-van Mölken, Johanna J.M. Takkenberg. Contemporary outcomes after surgical aortic valve replacement with bioprostheses and allografts: a systematic review and meta-analysis. *EJCTS*. 2016;50(4):605-616

Melinde R.S. Boland, Annemarije L. Kruis, **Simone A. Huygens**, Apostolos Tsiachristas, Willem J.Jl Assendelft, Jacobijn Gussekloo, Coert M.G. Blom, Niels H. Chavannes & Maureen P.M.H. Rutten-van Mölken. Exploring the variation in implementation of a COPD disease management programme and its impact on health outcomes: a post hoc analysis of the RECODE cluster randomised trial. *npj Primary Care Respiratory Medicine*. 2015(25):15071.

K. M. Holtzer-Goor , J. G. Gaultney, P. van Houten, A. S. Wagg, **S. A. Huygens**, M. M. J. Nielen, C. P. Albers-Heitner, W. K. Redekop, M. P. Rutten-van Mölken, M. J. Al. Cost-Effectiveness of Including a Nurse Specialist in the Treatment of Urinary Incontinence in Primary Care in the Netherlands. *PLOS ONE*. 2015. https://doi.org/10.1371/journal.pone.0138225