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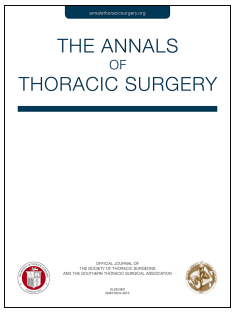


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# What is the potential of tissue-engineered pulmonary valves in children?

Running Head: Early HTA tissue-engineered pulmonary valves

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## 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.

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.

## PATIENTS AND 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 (Supplemental Table S1).(11) The number of 25,000 sampled patients was required to get stable results. For each patient, mortality and events within thirty 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 (Supplemental 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/Supplemental 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; Supplemental 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.

*Costs*

Healthcare costs included intervention, treatment of events and other healthcare use costs (Supplemental Table S3). Most costs were dependent on patient and intervention characteristics using (multilevel) generalised linear models ((M)GLM)(Supplemental Table S4; supplemental material reviewers only).(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 (Supplemental 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 (Supplemental 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 andeffects, and the

incrementalcost-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 4). 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 3).

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 (Supplemental 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 Supplemental Table S5. 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).

Supplemental 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.

*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 (Supplemental 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. 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/Supplemental 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 (Supplemental Figures S3-4).

## COMMENT

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.

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## TABLES

**Table 1. Pooled estimates of patient characteristics and outcomes after RVOTR.**

| | ≤2 years | | | >2 years | | |
|---|---|---|---|---|---|---|
| | **Meta-analysis** | **Included studies(n)** | **I2, %(χ2 P-value)** | **Meta-analysis** | **Included studies(n)** | **I2, %(χ2 P-value)** |
| **Study characteristics** | | | | | | |
| **No. of studies** | 19 | | | 37 | | |
| **No. of patients** | 1270 | 19 | | 6088 | 37 | |
| **Mean follow-up, years±SD** | 8.0±3.8 | 22 | | 5.7±3.5 | 41 | |
| **Patient and intervention characteristics** | | | | | | |
| **Mean age, years±SD** | 0.5±0.3 | 22 | | 7.3±8.2 | 41 | |
| **Male, n(%)** | 248(51.4) | 10 | | 2110(57.4) | 28 | |
| **Mean weight, years±SD** | 5.4±1.7 | 20 | | 22.5±15.1 | 23 | |
| **Etiology** | | 22 | | | 40 | |
| Tetralogy of Fallot(TOF) | 183(14.6) | | | 2235(42.5) | | |
| Trucus arteriosus communis(TAC) | 836(66.5) | | | 687(13.1) | | |
| Transposition great arteries(TGA) | 15(1.2) | | | 245(4.7) | | |
| TGA + ventricular septal defect(VSD) + pulmonary stenosis(PS) | 11(0.9) | | | 182(3.5) | | |
| Double outlet right ventricle(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 | |
| Polytetrafluoroethylene(PTFE) | - | 16 | | 1098(17.1) | 27 | |
| **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 reintervention | 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 reinterventions | | | | | | |
| - 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) |

**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 |

*Results of subgroup analyses can be found in table S6-7.

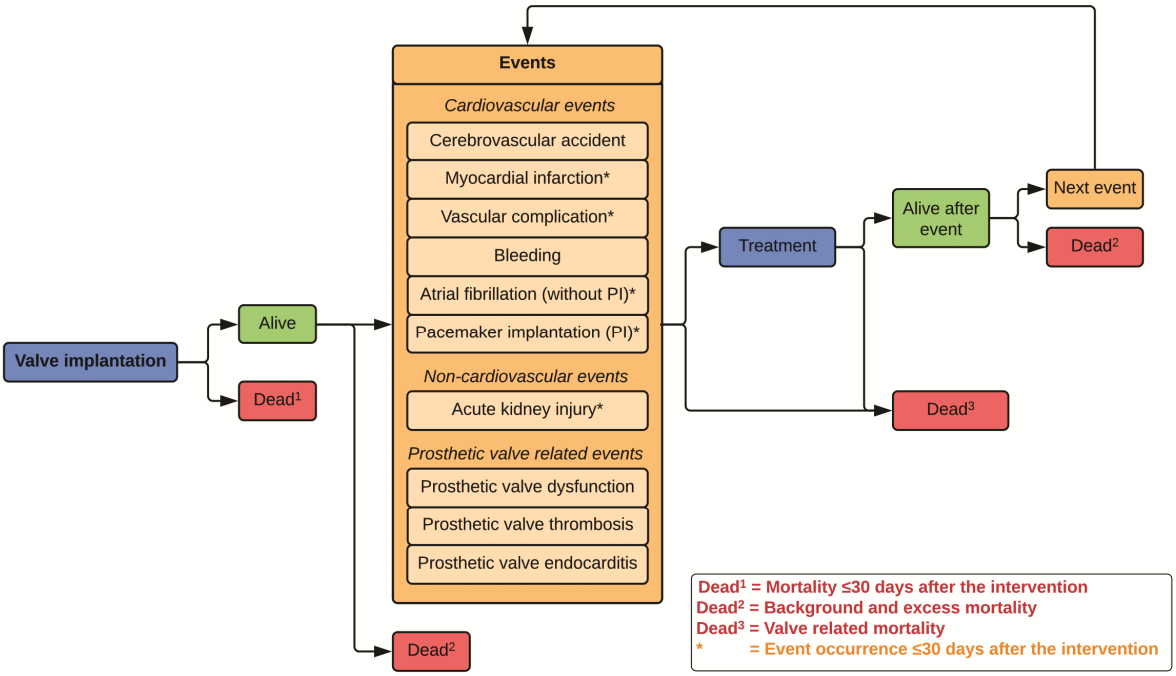
## FIGURE LEGENDS

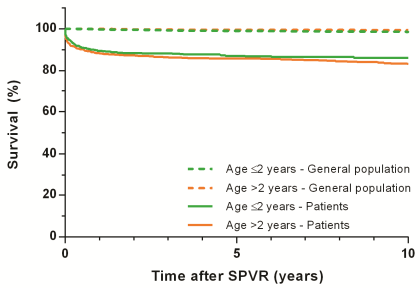
Figure 1. Conceptual model

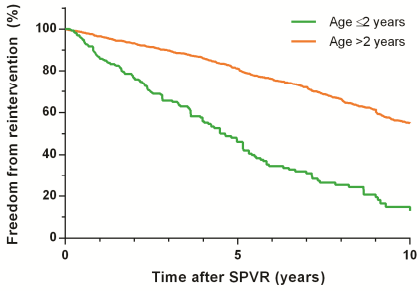
Figure 2. Pooled Kaplan-Meier survival and freedom from re-intervention (both surgical and percutaneous re-intervention) curves. Survival curve of general population was based on weighted survival tables from Europe, United States, and Asia for the pooled median year of intervention among included studies (2001) at the same mean age and proportion of males imported in the microsimulation model with valve-related mortality and events set to zero. (20, 21)

Figure 3. Probabilistic sensitivity analyses of RVOTR with TEHV ('improved performance' scenario) compared to existing heart valve substitutes. Incremental: difference between RVOTR with TEHV and existing heart valve substitute. QALY: quality-adjusted life year.

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.






| Number of patients at risk | | |
|---|---|---|
| 1008 | 386 | 144 |
| 2600 | 1030 | 591 |
| Pooled survival probabilities, patients (general population) | | |
| 100% (100%) | 87.1% (98.9%) | 86.1% (98.5%) |
| 100% (100%) | 85.7% (99.5%) | 83.2% (99.3%) |

| Number of patients at risk | | |
|---|---|---|
| 386 | 69 | 9 |
| 2414 | 1146 | 464 |
| Pooled survival probabilities | | |
| 100% | 46.1% | 14.9% |
| 100% | 81.1% | 55.0% |