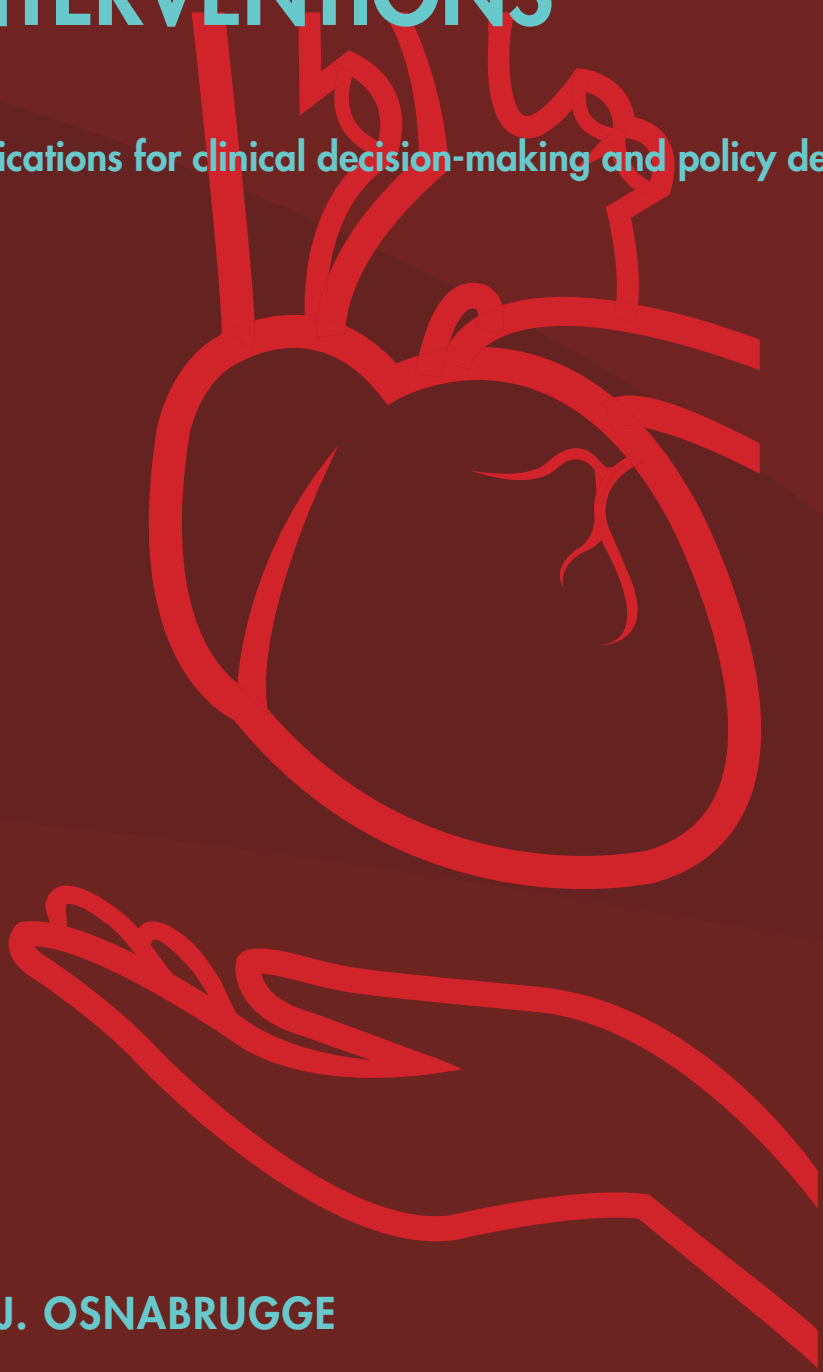
COSTS, QUALITY AND VALUE IN CARDIOVASCULAR INTERVENTIONS

Implications for clinical decision-making and policy development



R.L.J. OSNABRUGGE

Costs, Quality and Value in Cardiovascular Interventions

Implications for clinical decision-making and policy development

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Cover design: Studio Nilsson
Layout and printing: Optima Grafische Communicatie, Rotterdam, the Netherlands

ISBN: 978-94-6169-612-0

Costs, Quality and Value in Cardiovascular Interventions

Implications for clinical decision-making and policy development

Kosten, Kwaliteit en Waarde van Cardiovasculaire Interventies

Implicaties voor klinische en beleidsmatige besluitvorming

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the rector magnificus

prof.dr. H.A.P. Pols

and in accordance with decision of the Doctorate Board.
The public defence shall be held on

Wednesday the 25th of February 2015 at 1:30 pm

by

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The research in this thesis was partially financially supported by a Fulbright Scholarship, awarded by the J. William Fulbright Foreign Scholarship Board and The Bureau of Educational and Cultural Affairs of the United States Department of State.

Financial support by the Dutch Heart Foundation and H. Huysmans Foundation for the publication of this thesis is gratefully acknowledged.

For my dear parents

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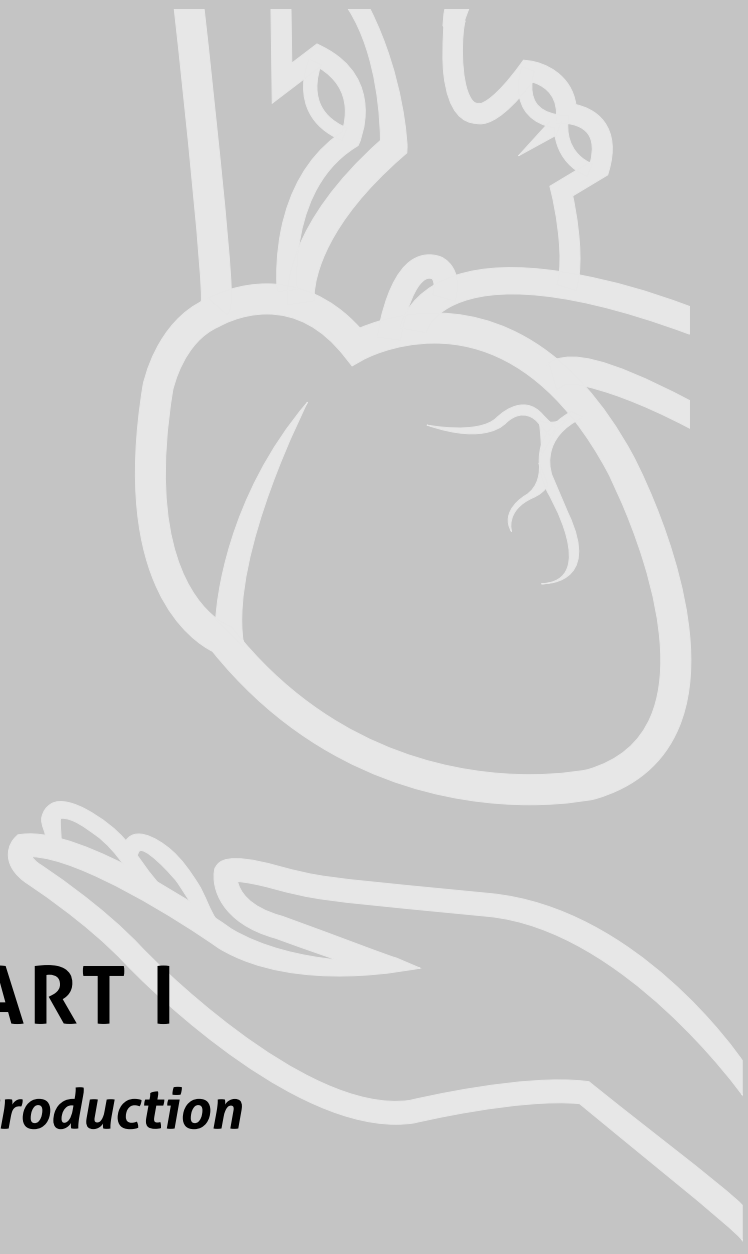

PART I

Introduction

CHAPTER 1

General Introduction Aims and Outline

GENERAL INTRODUCTION

Over the last several decades, the growth of health care expenditures in developed countries has consistently outpaced overall economic growth (Figure 1). Currently, health care expenditures represent 10-12% of the gross domestic product in many western European countries, while this proportion is nearly 18% in the United States.[2]

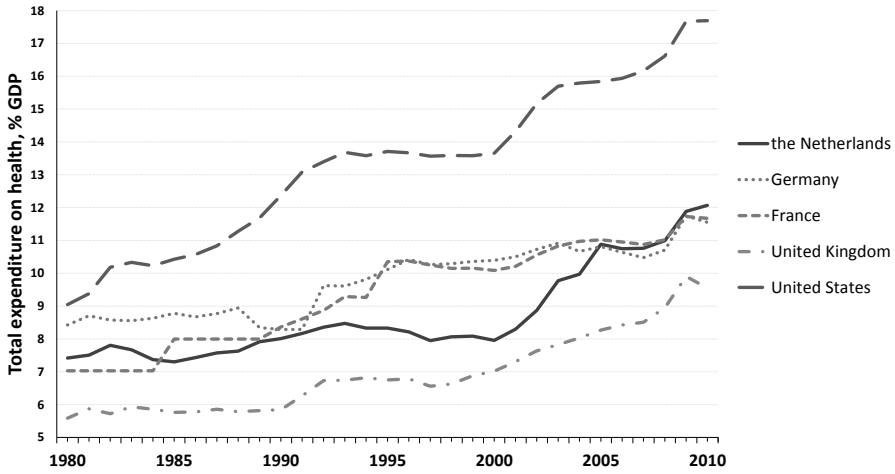

Figure 1. Trend in Health Care Expenditure as a Percentage of Gross Domestic Product, 1980-2010[2]

Moreover, more than 9% the total health care budget is spent on cardiovascular diseases, making it the second most expensive diagnosis group (Figure 2).[1]

The unsustainable trend of increasing health care costs threatens the financial stability of governments and necessitates difficult resource allocation decisions by policy-makers and physicians:

> *"It's not the investments that we've made to rescue our economy during this crisis. By a wide margin, the biggest threat to our nation's balance sheet is the skyrocketing cost of health care. It's not even close."*
>
> Atul Gawande, 2009

To inform medical decision-making and health care policy, clinical outcomes, quality of life and cost data need to be evaluated together. Quality of life and health economic studies aim to provide such information. The main drivers of rising healthcare costs are the aging population and the continued development of costly new technologies,[3] including new therapies for aortic stenosis and coronary artery disease.

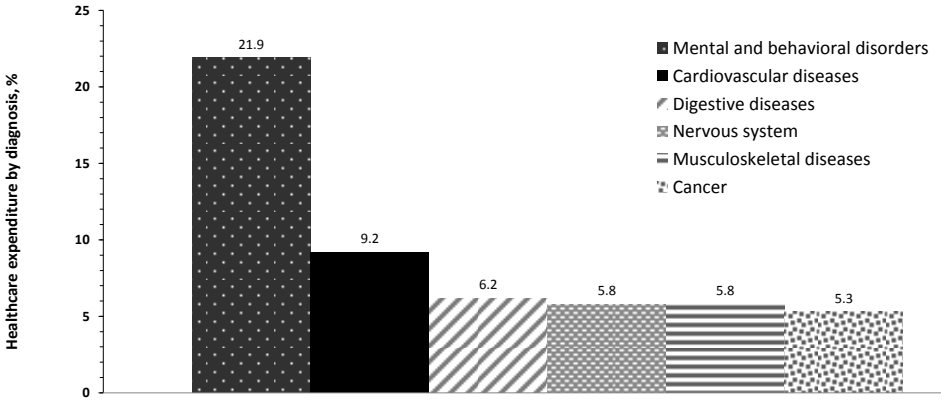

Figure 2. Health Care Expenditure in the Netherlands according to Main Disease Category, 2011[1]

AIMS

The aim of this thesis is to study the clinical, economic and quality-of-life considerations for clinical decision-making and policy development in cardiovascular interventions.

More specifically the goals are:

1. To investigate the disease prevalence, adoption trends, quality of life, and economic aspects associated with therapies of aortic stenosis.
2. To explore the economic and policy aspects of alternative revascularization therapies for coronary artery disease.
3. To study the performance of risk prediction models in cardiovascular clinical decision-making.
4. To appraise and improve the methodology of cardiovascular research, including systematic reviews, cost-effectiveness analyses, and observational studies.

OUTLINE

Within the preface, **Chapters 2 and 3** introduce the reader to alternative therapies for aortic stenosis (Part I) and coronary artery disease coronary revascularization (Part II), respectively. The current status of clinical, economic and quality of life considerations for these two cardiovascular diseases is discussed. Moreover, several risk scores, the influence of results on clinical practice and policy, and the appropriateness of the revascularization method are introduced.

Part II. Aortic Stenosis

The first part of this thesis focuses on the disease prevalence, adoption trends, quality of life and economic aspects of therapies for severe aortic stenosis. First, the disease prevalence of severe aortic stenosis and the potential number of candidates for transcatheter aortic valve implantation (TAVI) are studied (**Chapter 4**). The actual adoption of TAVI in Europe and factors influencing device utilization are evaluated in **Chapter 5**. In **Chapter 6**, quality of life after TAVI is assessed in patients that were at extreme risk for surgical aortic valve replacement (SAVR). Subsequently, the costs associated with SAVR and TAVI are studied. The costs of SAVR according to pre-operative risk categories are evaluated in **Chapter 7**. In **Chapter 8** costs and resource use associated with TAVI and SAVR are compared in a propensity-matched cohort of intermediate risk patients. **Chapter 9** discusses controversies on the (cost-)effectiveness of TAVI. The final chapter of this part reviews non-cardiac surgery in patients with severe aortic stenosis (**Chapter 10**).

Part III. Coronary Revascularization

The second part concerns economic and policy aspects of alternative revascularization therapies for coronary artery disease. In **Chapter 11** the long-term clinical benefits and cost-effectiveness of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) with drug-eluting stents (DES) are studied from a U.S. health care perspective. **Chapter 12** aims to evaluate the lifetime cost-effectiveness of CABG versus DES-PCI from a European perspective, thereby also assessing the discriminative power of a new risk score that incorporates both pre-operative clinical risk factors and the anatomical complexity of coronary artery disease. Subsequently, **Chapter 13** describes a prediction model for costs and length of stay after CABG. These models are applied in **Chapter 14** to compare costs, quality and value of CABG across centers. In **Chapter 15**, the appropriate application of guidelines and evidence based medicine is discussed for both CABG and PCI.

Part IV. Risk Prediction in Cardiac Surgery

In this part we compare the performance of U.S. and European risk prediction models for cardiac surgical procedures, including CABG, SAVR, and mitral procedures (**Chapter 16**). **Chapter 17** concerns a comprehensive systematic review describing traditional and novel risk factors for death, stroke, renal failure and prolonged length of stay after cardiac surgery. **Chapter 18** reflects on long-term prediction models for CABG and PCI.

Part V. Methodological Appraisal of Cardiovascular Research

The last part of this thesis is an appraisal of several methodological aspects in cardiovascular research. **Chapter 19 and 20** critically appraise the association between *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel. **Chapter 21** reviews the

current practice of systematic reviews and meta-analyses in the cardiovascular field and provides recommendations for improvement. Subsequently we critically appraise the methodology of an observational study (**Chapter 22**), a cost-effectiveness analysis (**Chapter 23**), and a clinical trial (**Chapter 24**).

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CHAPTER 2

Therapies for Aortic Stenosis

Based on:
Cost-Effectiveness of Transcatheter Valvular Interventions: Economic Challenges

Osnabrugge RL, Kappetein AP, Reynolds MR, Cohen DJ.

EuroIntervention. 2013;9 Suppl:S48-54.

Aortic stenosis (AS) is the most common valvular heart disease in developed countries, and its burden of disease is expected to increase due to population aging.[1] Until recently, surgical aortic valve replacement (SAVR) was the only treatment option in patients with severe AS, with approximately 67,500 SAVRs performed each year in the US alone.[2] Consequently, also the economic burden of treating this disease is substantial.

One of the most promising advances in cardiovascular medicine in recent years has been the development of safe and reliable catheter-based techniques for treatment of valvular heart disease.[3] However, the rapid development and widespread application of transcatheter aortic valve implantation (TAVI) for treatment of patients with calcific AS has raised important questions about the value of these technologies.[4] Given the high cost of these therapies as well as the growing population of potential candidates, it is clear that therapies such as TAVI require not only clinical evaluation, but also careful

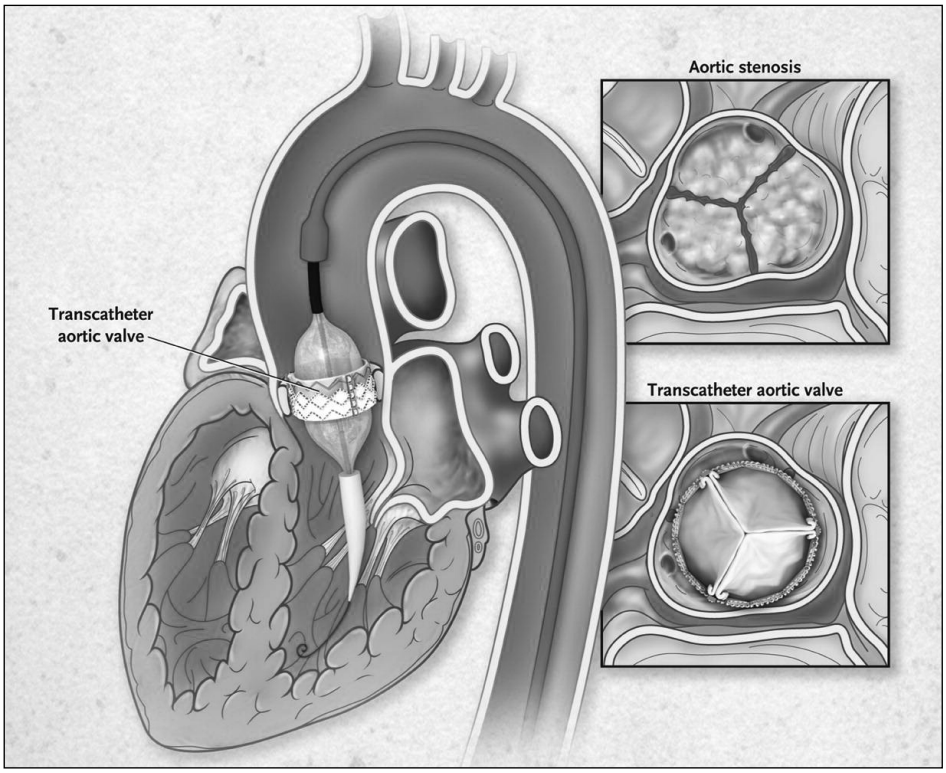

Figure 1. Graphical Representation of Transcatheter Aortic Valve Implantation
Graphical representation of Transcatheter Aortic Valve Implantation (TAVI) for the treatment of severe Aortic Stenosis. After retrograde advancing the transcatheter valve from the insertion in the femoral artery across the aortic arch, the valve is positioned at the level of the native aortic valve. This type of transcatheter valve is deployed by inflating a balloon during a brief period of rapid ventricular pacing. Reproduced with permission from Smith et al.,[17] Copyright Massachusetts Medical Society.

economic evaluation. Cost-effectiveness analysis is a formal approach to these issues that seeks to inform both medical decision-making and health care policy by comparing the benefit of a new therapy with its costs.

COST-EFFECTIVENESS OF TAVI VERSUS MEDICAL THERAPY

Several studies have examined the cost-effectiveness of TAVI versus optimal medical management in inoperable patients (Table 1).[5-11] The analyses represent a broad range of healthcare systems and incorporate different modeling methodologies, willingness-to-pay-thresholds, and discount rates. An individual patient cost-effectiveness analysis based on Cohort B of the Placement of Aortic Transcatheter Valves (PARTNER) trial estimated an incremental cost-effectiveness ratio (ICER) of $50 212 per life-year gained (Figure 2).[9] Other studies have used Markov models (generally based on the aggregate PARTNER B outcomes and survival data) and reported incremental cost-effectiveness ratios ranging from £16 200 (approx. $25 000) per quality-adjusted life-year (QALY)

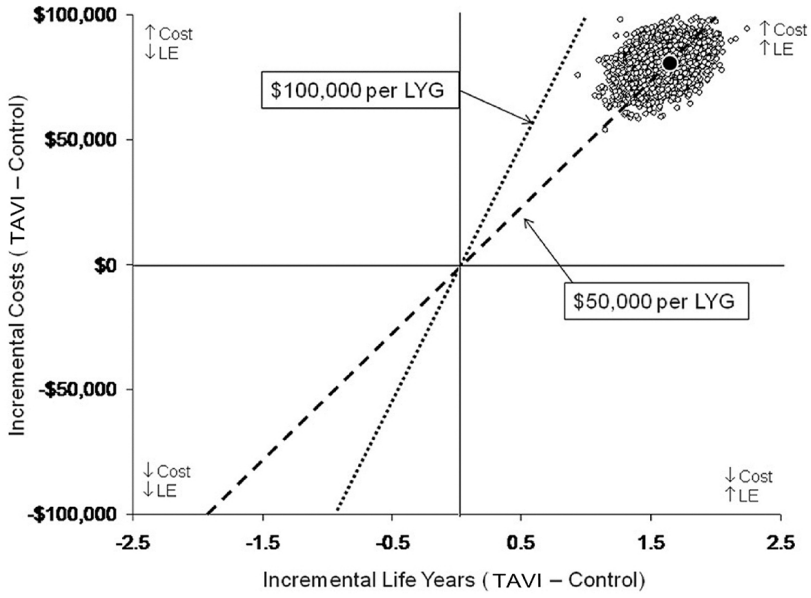

Figure 2. Cost-Effectiveness Results of PARTNER Cohort B: TAVI versus Standard Therapy
The mean incremental cost-effectiveness ratio of TAVI versus standard therapy is plotted as the dark circle, along with 5000 bootstrap replications (cloud of circles). In this cost-effectiveness plane the incremental cost-effectiveness ratio is expressed in US $ per life-year gained. The two dashed lines represent two willingness-to-pay thresholds of $100 000 or $ 50 000 per LYG.
LE, life-expectancy; LYG, life-years gained; TAVI, transcatheter aortic valve implantation. Reprinted with permission from Reynolds et al.[9]

Table 1. Economic Studies comparing TAVI versus Standard (Medical) Therapy

Author	Year	Country	Methods	Horizon	Comparison	Crude Δcost (TAVI-ST)	Crude ΔQALY (TAVI-ST)	ICER (per QALY)	WTP threshold (per QALY)	Probability that TAVI is cost-effective
Reynolds[9]	2012	USA	Trial + projections	Lifetime	TF-TAVI vs. ST	$79837	1.30	$61889	$50000 $100000	3% 100%
Gada[7]	2012	USA	Model	Lifetime	TF-TAVI vs. ST	NR	NR	$39964	$100000	NR
Gada[6]	2012	USA	Model	Lifetime	TF-TAVI vs. ST	NR	NR	$44384	$100000	NR
Doble[5]	2012	Canada	Model	20 year	TF-TAVI vs. ST	C$31018	0.60	C$51324	C$49000	44.1%
Hancock[8]	2013	Canada	Model	3 year	TF-TAVI vs. ST	C$15687	0.49	C$32170	C$50000	92%
Watt[10]	2011	UK	Model	Lifetime	TF-TAVI vs. ST	£25200	1.56	£16200	£20000 £30000	100% 100%
Neyt[11]	2012	Belgium	Model	Lifetime	TF-TAVI vs. ST	€33200	0.74	€44900	€22800 €34200	9.2% 36.7%

C$, Canadian dollars; ICER, incremental cost-effectiveness ratio; NR, not reported; QALY, quality-adjusted life year; ST, standard therapy; TAVI, transcatheter aortic valve implantation; TA-TAVI, TAVI via transapical access; TF-TAVI, TAVI via transfemoral access; USA, United States of America; UK, United Kingdom; WTP, willingness-to-pay.

gained to $61 889 per QALY.[5-8, 10, 11] Despite underlying differences in methodology and healthcare systems across these studies, the relatively consistent results lead to the conclusion that TAVI is economically attractive compared with medical management in patients who are not candidates for surgery. In other words, the increased life expectancy and quality-adjusted life expectancy after TAVI is achieved at an incremental cost that is, for most countries, within the range of other accepted therapies.

In addition to the general finding that TAVI is reasonably cost-effective for inoperable patients with severe AS, several broad themes have emerged from these studies. The first is that for patients who are considered inoperable, TAVI results in higher overall healthcare costs. In fact, even if the TAVI prosthesis were provided free of charge, overall healthcare expenditures would be increased.[9] This finding reflects the fact that inoperable patients with severe AS have very a relatively short life expectancy (median survival <2 years), which is prolonged substantially if they undergo TAVI. The second factor that underlies this conclusion is the finding that even after successful TAVI, patients who were otherwise inoperable continue to accrue substantial healthcare related costs (on the order of $30,000 per year) due to their severe comorbidity. Thus, by extending their lives, the net cost to the healthcare system actually increases.

The second general conclusion to be drawn from these studies is that in order for TAVI to be cost-effective in inoperable patients with AS, it must result in substantial gains in life expectancy (in the order of one to two years minimum) as well as improved quality of life.[9] Sensitivity analyses based on the PARTNER trial demonstrate that if quality of life did not improve after TAVI (but survival did improve), the ICER for TAVI compared with medical therapy would increase to ~$80,000 per quality-adjusted life year (QALY) gained—a value that exceeds societal willingness to pay levels in many Western societies.[12]

COST-EFFECTIVENESS OF TAVI VERSUS SAVR

In Cohort A of the PARTNER trial, 699 patients at high surgical risk were randomized to TAVI via either a TF or TA approach or SAVR. Over a two-year follow-up period, there was no difference in survival comparing TAVI with SAVR (66.1% vs. 65.0%, $p = 0.78$).[13] Thus, in contrast to the results of TAVI in inoperable patients, among high risk but operable AS patients, the main benefit of the less invasive procedure is in quality of life. Indeed, a formal quality of life study conducted alongside PARTNER Cohort A demonstrated that TAVI did result in improved quality of life compared with SAVR in the short term, but that these benefits were restricted to patients who were eligible for a transfemoral TAVI (TF-TAVI) procedure and were limited to the first six months of follow-up.[14] In contrast,

among patients who were only suitable for TA access, there were no quality of life benefits with TAVI compared with SAVR, and there were trends toward worse quality of life at the 1 and 6 month assessments.[14] Given these findings, it is not surprising that when these results were expressed in quality-adjusted life years for the purpose of economic analysis, TF-TAVI was associated with a small but significant gain of 0.068 QALYs (95% CI, 0.017-0.1230) over the first year of follow-up, whereas in the TA subset, TAVI was associated with a loss of 0.070 QALYs compared with SAVR (95% CI, −0.151-0.012).[15] With comparable survival and only small differences in quality of life, costs thus play a pivotal role in the cost-effectiveness of TAVI when compared with SAVR.

Table 2 provides an overview of the published studies that have investigated the cost-effectiveness of TAVI vs. surgical aortic valve replacement (SAVR) for patients at high risk of mortality from SAVR.[5-7, 11, 15, 16] From the US perspective, individual patient cost-effectiveness analysis of Cohort A in the PARTNER trial showed that TF-TAVI route was an economically attractive strategy compared with SAVR with lower one-year costs and greater quality adjusted life expectancy (Figure 3). In contrast, transapical TAVI (TA-TAVI) was associated with higher costs and lower quality-adjusted life expectancy, rendering it both clinically and economically unfavorable relative to SAVR. Gada and colleagues

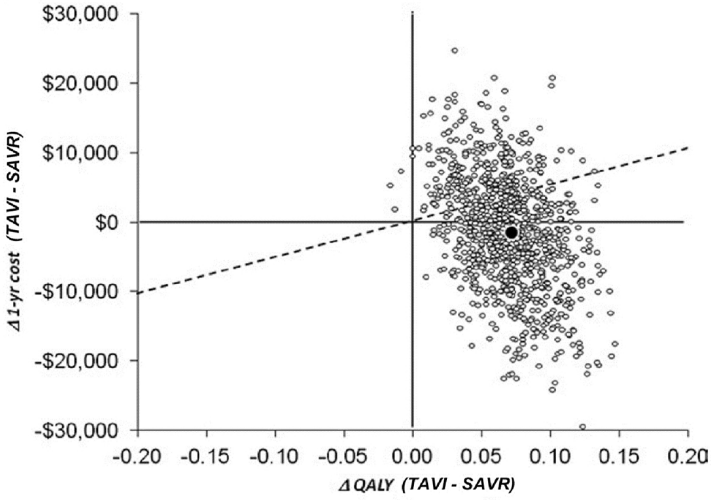

Figure 3. Cost-Effectiveness Results of PARTNER Cohort A: TAVI versus SAVR
The mean incremental cost-effectiveness ratios for transfemoral TAVI versus SAVR are plotted as dark circles. The cloud of open circles represents each of the individual 1000 bootstrap replications based on the observed trial results. The dashed line represents a willingness-to-pay threshold of $50 000 per QALY gained. In this base-case analysis, TF-TAVI was associated with a gain of 0.068 QALYs and cost savings of $1 250 per patient, leading to a position of economic dominance. SAVR, surgical aortic valve replacement TF-TAVI, TAVI via transfemoral access; TAVI, transcatheter aortic valve implantation; QALY, quality-adjusted life-year. Reprinted with permission from Reynolds et al.[15]

Table 2. Economic Studies comparing TAVI versus Surgical Aortic Valve Replacement

Author	Year	Country	Methods	Horizon	Comparison	Crude Δcosts (TAVI-SAVR)	Crude ΔQALY (TAVI-SAVR)	ICER (per QALY)	WTP threshold (per QALY)	Probability that TAVI is cost-effective
Reynolds[8]	2012	USA	Trial	1 year	TAVI vs. SAVR TF-TAVI vs. SAVR TA-TAVI vs. SAVR	$2 070 -$1 249 $9 906	0.027 0.068 −0.070	$76 877 TAVI dominant TAVI dominated	$50 000 $50 000 $50 000	43.8% 70.9% 7.1%
Gada[12]	2012	USA	Model	Lifetime	TF-TAVI vs. SAVR	$3 164	0.06	$52 773	$100 000	NR
Gada[11]	2012	USA	Model	Lifetime	TA-TAVI vs. SAVR	$100	−0.04	TAVI dominated	$100 000	47%
Doble[10]	2012	Canada	Model	20 year	TAVI vs. SAVR	$11 153	−0.102	TAVI dominated	C$ 49 000	11.6%
Neyt[15]	2012	Belgium	Model	1 year	TAVI vs. SAVR	€20 400	0.03	$750 000	€22 800 €34 200	NR
Fairbairn[20]	2013	UK	Model	10 year	TAVI vs. SAVR	-£1 350	0.06	TAVI dominant	£20 000	64.6%

C$, Canadian dollars; ICER, incremental cost-effectiveness ratio; MM, medical management; NR, not reported; QALY, quality-adjusted life year; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TA-TAVI, TAVI via transapical access; TF-TAVI, TAVI via transfemoral access; USA, United States of America; UK, United Kingdom; WTP, willingness-to-pay

examined the cost-effectiveness of TA-TAVI using a disease simulation model and also concluded that it was economically dominated by SAVR.[6]

One interesting finding from the available literature is that even though most model-based cost-effectiveness analyses have used the PARTNER A trial as the key source for their base case assumptions, these studies draw markedly different conclusions that depend largely on the healthcare system in which the analysis is conducted.[5-7, 11, 16] For example, one model that incorporated a UK perspective found TAVI to be economically dominant compared with SAVR for high risk patients;[16] another model that considered a US perspective found that TF-TAVI was slightly more costly than SAVR but still cost-effective by conventional standards.[7] However, two studies that considered a Belgian and a Canadian perspective have concluded that TAVI is substantially more costly and only minimally more effective than SAVR, suggesting that TAVI is relatively unattractive from an economic standpoint for patients who are otherwise candidates for SAVR.

By far, the most important factor that explains these discrepant results is differences in the cost of high-risk SAVR in various healthcare settings. In countries where high-risk SAVR is quite costly (US, UK), it appears that the reductions in length of stay following TAVI result in substantial cost offsets to the healthcare system. In other settings (e.g., Canada, Western Europe), however, the costs of SAVR appear to be markedly lower. Whether these differences relate to true differences in health care costs across health systems or relate to differences in the types of patients that form the basis for the surgical cost estimates is unclear. One consistent finding from the available studies is that the cost-effectiveness of TAVI vs. SAVR depends on the access route. In particular, no study to date has demonstrated a favorable ICER for TAVI vs. SAVR among patients who are not suitable for transfemoral access. In general, these findings relate to the observations from the PARTNER A trial that TA-TAVI did not lead to measurable improvements in survival, quality of life, or length of stay compared with SAVR[14]. Since these results were derived from the very earliest US experience with TA-TAVI, however, it will be important to revisit these analyses as operator and institutional experience increases and also to assess whether other access routes (e.g., subclavian, direct aortic) might provide more favorable economic outcomes.

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CHAPTER 3

Coronary Revascularization

Based on:
Multivessel Coronary Artery Disease: quantifying how recent trials should influence clinical practice

Osnabrugge RL, Head SJ, Bogers AJ, Kappetein AP.

Expert Rev Cardiovasc Ther. 2013;11:903-18.

In the 1960s, the first saphenous vein bypass from the ascending aorta to the anterior descending coronary artery was performed,[1] thereby laying the foundation of coronary artery bypass grafting (CABG) and the treatment of coronary artery disease. CABG was quickly integrated in clinical practice, although the first trial comparing it to medical therapy was only published in 1983.[2] In 1977, Gruentzig performed the first percutaneous coronary intervention (PCI) by reopening coronary lesions with a distensible balloon.[3] Both PCI and CABG have since been considered for treatment of coronary artery disease. Nowadays, approximately 3700 individuals per million US adults undergo coronary artery revascularization with PCI, while 1100 undergo CABG.[4] The number of patients undergoing PCI remained constant between 2001 and 2008, whereas the number of CABGs dropped from 1700 per million US adults to 1100 in 2008.

CABG VERSUS MEDICAL THERAPY

Soon after the introduction of CABG, it quickly became apparent that it was successful in relieving angina pectoris.[1] It was, however, more difficult to prove that CABG prolonged life compared with medical therapy and thus randomized studies were performed in the 1970s and 1980s. The largest three studies included approximately 800 patients each[5-7] but were underpowered to detect small risk reductions.

In a collaborative meta-analysis, patient-level data of seven trials were pooled; 83% of the patients had MVD and were predominantly middle-aged males.[8] Only 10% of CABGs was performed with internal mammary grafts and 20% of the patients were treated with antiplatelet therapy. The meta-analysis showed that at 10 years, 41% of the medically managed group had undergone CABG surgery. Notably, there was a clear survival benefit for CABG compared with medical therapy at 5 years (10.2% vs. 15.8% mortality), 7 years (15.8% vs. 21.7% mortality) and 10 years (26.4% vs. 30.5% mortality). Since survival was particularly improved in patients with more extensive coronary artery disease, the meta-analysis also confirmed the hypothesis that the benefits of CABG are higher when the myocardium at risk is larger. Moreover, the advantages of surgery were not restricted to patients with left main coronary artery disease, but also applied to MVD patients. The current guidelines recommend CABG over optimal medical therapy (OMT) with a class I recommendation in the majority of patients with MVD.[9, 10]

CABG VERSUS PCI

Over the past two decades, almost 30 randomized controlled trials have investigated CABG versus PCI.[9, 11-13] Initially, CABG was compared with balloon angioplasty, then with BMS and most recently with drug-eluting stents (DES).

CABG versus Balloon Angioplasty or BMS

A meta-analysis of 23 randomized trials showed that survival at 1 and 5 years was similar in patients undergoing CABG or PCI (balloon angioplasty or BMS).[11] More specifically, in patients with MVD, survival at 5 years was 91% after CABG and 90% after PCI. There was no substantial difference between trials using balloon angioplasty versus trials using BMS (Table 1).[14-27]

Another collaborative meta-analysis pooled data of MVD patients from six CABG versus balloon angioplasty trials,[14-17, 19, 21] and four CABG versus BMS trials.[20, 24, 26, 27] At a median follow-up of 5.9 years, there was no difference in death (CABG 8% vs. PCI 10%) and the composite of death and MI (CABG 15% vs. PCI 17%; Figure 1).[28] There were more deaths and repeat revascularizations with CABG than with PCI (CABG 10% vs. PCI 25%). In addition, angina relief was greater with CABG (CABG 14% vs. PCI 26%).

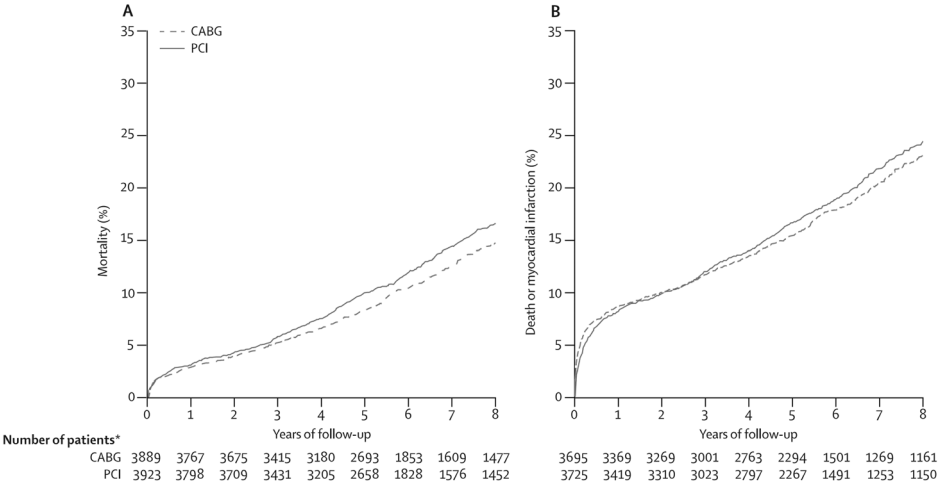

Figure 1. Outcomes of Treatment with CABG or PCI in ten Randomized Trials
Pooled data from 10 randomized trials show overall unadjusted mortality (A) and the composite endpoint of death or myocardial infarction (B) after randomization to CABG or PCI. Data on the composite endpoint was not available from the EAST trial.[21] *Number of patients available for follow-up.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention
Reproduced with permission from Hlatky et al.[28]

Table 1. Studies comparing CABG with Balloon Angioplasty/BMS in Patients with MVD

Study	Size, n	Age, y	Enrollment	Primary endpoint	Follow-up, y	CABG using arterial grafts,%	PCI using stents,%	5 year survival,%	
								PCI	CABG
GABI[19]	323	NR	1986-1991	Angina	13	37	0	93	95
EAST[45]	392	61	1987-1990	Death, MI	8	86	0	88	91
ERACI I[92]	127	58	1988-1990	Death, MI, Angina, Revascularization	3	77	0	NR	NR
BARI[16]	1829	61	1988-1991	Death	10	82	0	86	89
RITA I[87]	1011	57	1988-1991	Death, MI	6.5	74	0	95	95
CABRI[15]	1054	60	1988-1992	Death	1	81	0	NR	NR
Toulouse[17]	152	67	1989-1993	Angina	5	58	0	87	87
Balloon Overall								89	91
MASS II[99]	408	60	1995-2000	Death, MI, Repeat revascularization	5	92	68	86	84
AWESOME[22]	454	67	1995-2000	Death	5	76	54	79	73
ERACI II[24]	450	62	1996-1998	Death, MI, CVA, Repeat revascularization	5	89	100	93	88
SoS trial[27]	988	61	1996-1999	Repeat revascularization	3	93	100	NR	NR
ARTS I[26]	1205	61	1997-1998	Death, MI, CVA, Repeat revascularization	5	93	100	92	92
Octostent[18]	280	60	1998-2000	Death, MI, Repeat revascularization	1	100	100	NR	NR
Myoprotect I[23]	44	70	1998-2001	Death, MI, Repeat revascularization	1	NR	100	NR	NR
BMS Overall								91	89

Adapted from Bravata et al.[11]

ARTS, Arterial Revascularization Therapies Study; AWESOME, Angina with Extremely Serious Operative Mortality Evaluation; BARI, Bypass Angioplasty Revascularization Investigation; CABG, coronary artery bypass grafting; CABRI, Coronary Angioplasty versus Bypass Revascularization Investigation; EAST, Emory Angioplasty versus Surgery Trial; ERACI, Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease; GABI, German Angioplasty Bypass Surgery Investigation; MASS, Medicine, Angioplasty, or Surgery Study; MVD, multivessel disease; n, number of participants; NR, not reported; PCI, percutaneous coronary intervention; Ref, reference; RITA, Randomized Intervention Treatment of Angina; SoS, Stent or Surgery; y, years.

CABG versus DES

To reduce the high rate of restenosis and repeat revascularization, the DES was developed and introduced commercially in 2002. The coating of the stent contains a powerful immunosuppressive drug that should prevent restenosis and thereby the need for repeat revascularization. A meta-analysis showed that DES are indeed more effective in reducing restenosis compared with BMS.[29]

With the introduction of DES, a new era of comparisons between CABG and PCI started. A meta-analysis of nine observational, nonrandomized studies compared CABG with DES in 24,268 patients with MVD.[30] At 20 months, the incidence of the composite end point of death, acute MI and cerebrovascular accidents was similar between the two treatments. Importantly, however, there was a significantly higher risk of repeat revascularization in the PCI group (HR: 4.06; $p < 0.001$).

The SYNTAX trial is the most important trial that randomized patients to CABG or PCI with DES.[31, 32] The trial was set-up as an all-comers study and patients with three-vessel and/or left main disease were discussed in the heart team with the local cardiac surgeon and interventional cardiologist. At 5 years, the composite primary end point of death from any cause, stroke, MI or repeat revascularization occurred less often with CABG compared with PCI (CABG 26.9% vs. PCI 37.3%; $p < 0.001$; Figure 2). This difference was mainly driven by a higher rate repeat revascularization in PCI (CABG: 13.7% vs. 25.9%; $p < 0.001$), but also MI (CABG 3.8% vs. PCI 9.7%; $p < 0.001$) occurred more often with PCI compared with CABG. The hypothesis-generating subgroup of 1095 patients with three vessel disease showed a similar picture with a 5-year rate of the composite primary end point that was lower in CABG (CABG: 24.2% vs. PCI: 37.5%; $p < 0.001$).[31, 33] Moreover, survival at 5 years was better with surgery (CABG 9.2% vs. PCI 14.6%; $p = 0.006$).[31] The trial also introduced the SYNTAX score. This measure of coronary complexity showed significant interaction with clinical outcomes; CABG was better in patients with more complex coronary anatomy, whereas PCI proved to be an acceptable revascularization in anatomically less complex disease. Also in the three-vessel cohort, the difference in the rates of the composite end point increased according to the SYNTAX score categories (low: PCI 33.3% vs. CABG 26.8%, $p = 0.21$; intermediate: PCI 37.9% vs. CABG 22.6%, $p = 0.0008$; high: PCI: 41.9% vs. CABG 24.1%, $p = 0.0005$). Using both the randomized and registry data, the conclusion was that CABG offers a survival advantage and reduction in repeat revascularization in almost 79% of all patients with three-vessel disease.[34]

Two large registries used comparative effectiveness methodology to validate the SYNTAX results in real-world clinical practice. They provided supportive evidence for a survival benefit with CABG.[35, 36] In New York State, adverse outcomes (death, death or MI and repeat revascularization) with CABG and PCI with DES were compared in almost 18,000 patients with MVD.[36] At 18 months follow-up, patients who underwent surgery had lower rates of repeat revascularization (CABG 5.2% vs. PCI 30.6%; $p < 0.001$). Moreover, CABG was associated with greater adjusted survival (CABG 94.0% vs. PCI 92.7%; $p = 0.03$) and the end point freedom of death and MI (CABG 92.1% vs. 89.7%; $p < 0.001$). In the American College of Cardiology Foundation (ACCF) and Society of Thoracic Surgeons (STS) Database Collaboration on the ASCERT study, more than 180,000 patients from

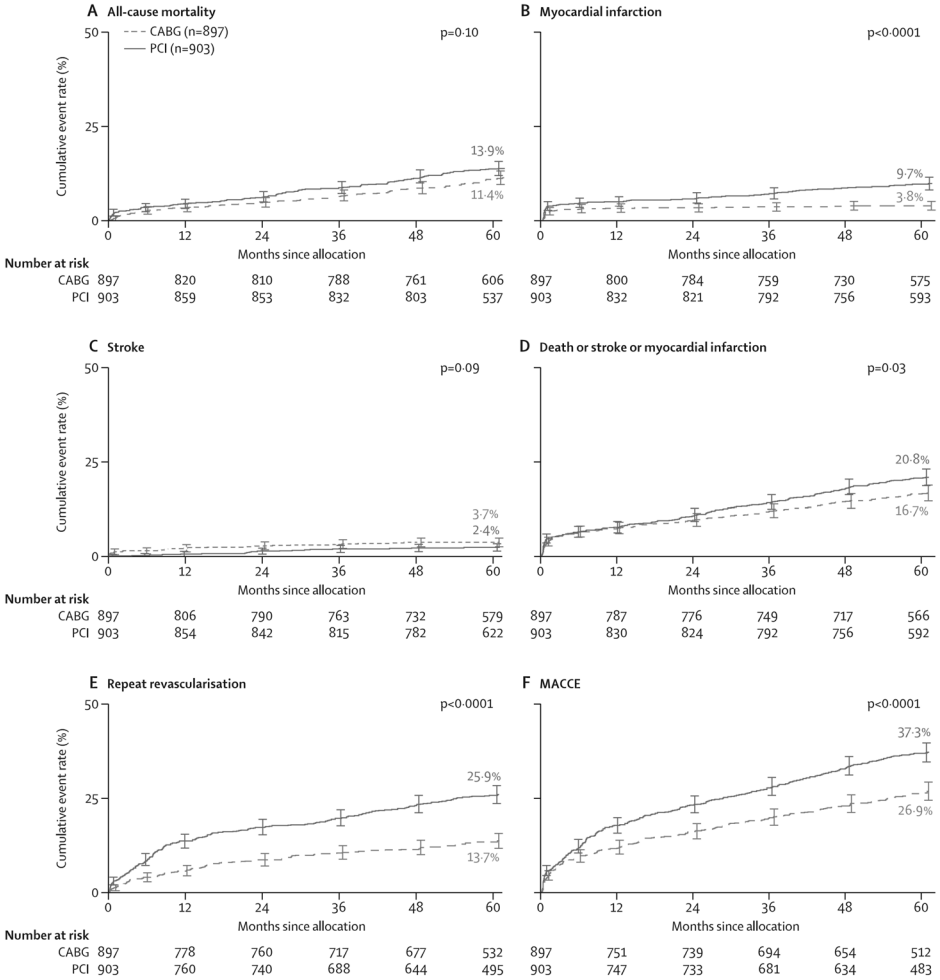

Figure 2. SYNTAX trial 5-year Kaplan-Meier cumulative Event Curves
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MACCE, major adverse cardiac and cerebrovascular events.
Reproduced with permission from Mohr et al.[31]

the ACCF NCDR and STS Adult Cardiac Surgery databases were linked with data from the Centers for Medicare and Medicaid Services for the years 2004 through 2008.[35] Mean age was 74 years and all patients had two- or three-vessel disease. At 1 year, there was no significant difference in adjusted mortality between groups (CABG 6.2% vs. PCI 6.6%; risk ratio: 0.95; 95% CI: 0.90–1.00). At 4-year follow-up, however, there was significantly lower mortality with surgery compared with PCI (CABG 16.4% vs. 20.8%; risk ratio: 0.79; 95% CI: 0.76–0.82).

In summary, data from registries and the SYNTAX trial show that there is sufficient evidence to state that in the majority of patients with MVD, CABG outperforms PCI with regard to long-term survival, MI and repeat revascularization. This evidence is reflected in the recommendations by the European and American guidelines on myocardial revascularization that CABG has a class I recommendation for the majority of patients with MVD, whereas PCI has a class IIa/b recommendation.[9, 10]

A potential explanation for the survival benefit is that diffuse atherosclerosis is bypassed with one or two grafts to the mid-coronary vessel, providing extra sources of blood flow to the myocardium.[37] This results in protection of the entire distal myocardium for current and future proximal obstructive disease. Stents, however, aim to restore the native vessel without protection against new proximal disease. In addition, multiple stents are needed in diffuse disease each with its own risks of restenosis.

The evidence from trials and registries have resulted in class Ia recommendations for CABG over PCI in the majority of patients with stable coronary artery disease.[9, 10] By randomizing 2600 patients with left main, or left main-equivalent disease to CABG or PCI with DES, the XIENCE the EXCEL trial is expected to provide additional insights on the optimal revascularization strategy (ClinicalTrials.gov identifier: NCT01471522205776).

DIABETICS

In patients with diabetes mellitus (DM), the process of atherosclerosis is accelerated through prothrombotic and proinflammatory states in combination with endothelial dysfunction and metabolic disorders.[38] Although the benefits of glycemic control on microvascular problems of DM have been demonstrated in clinical trials, the evidence for benefits of lowering HbA1c levels on cardiovascular disease is less proven.[9] Therefore, and because of the high prevalence of diabetes, these patients form a specific group of interest in the revascularization debate.[39, 40] Indeed, a Danish cohort study showed that patients with DM, but without a history of coronary artery disease, had a similar 5-year cardiac mortality risk as non-DM patients with a history of MI.[41]

Revascularization versus Medical Therapy in Diabetics

There are two major trials comparing the outcomes of revascularization and medical therapy in diabetics.[42, 43] The BARI-2D trial was a dedicated trial in which 2368 diabetics were randomized between medical therapy and revascularization (PCI or CABG).[42] At 5 years, there was no difference in the rate of survival (revascularization 88.3% vs. medical therapy 87.8%; $p = 0.97$) and the composite of death, MI or stroke (revascularize-

tion 77.2% vs. medical therapy 75.9%; $p = 0.70$). A subgroup analysis of the COURAGE trial showed that PCI coupled with OMT did not reduce the rate of adverse events as compared with OMT alone.[43]

CABG versus PCI in Diabetics

The BARI trial provided the first evidence that patients with DM had better survival after CABG than after PCI.[16] Initially, these results were not replicated in other trials,[44-46] but a meta-analysis with pooled data from ten randomized trials showed that 23% of the 615 diabetics assigned to CABG and 29% of the 618 diabetics assigned to PCI died.[28] In the patients without DM, 13% and 14% died in the CABG and PCI group, respectively ($p = 0.014$ for interaction). This interaction remained after adjustment for other patient characteristics ($p = 0.008$).

In a subgroup of 452 DM patients from the SYNTAX trial, those who underwent PCI had a higher risk of the composite of death, MI, stroke and repeat revascularization at 5 years (CABG 46.5% vs. PCI 29.0%; $p < 0.001$). This difference was driven by a significant difference in repeat revascularization (CABG 14.6% vs. PCI 35.3; $p < 0.001$),[47] while the other individual outcomes were similar. Similar to the overall cohort of the trial, the difference between PCI and CABG in diabetics increased according to the SYNTAX score.

The CARDIa trial randomized 510 patients with DM and multivessel or complex single-vessel disease to either CABG or PCI.[48] At 1 year, there was no difference in the composite primary end point of death, MI and stroke (CABG 10.5% vs. PCI 13.0%; $p = 0.39$). However, the trial was underpowered and only 69% of patients underwent PCI with DES, while the remaining 31% received BMS.

Recently, the results of the FREEDOM trial were published.[49] In this trial, 1900 patients with DM and MVD were randomized to undergo either PCI with DES or CABG. At 5 years, the primary composite outcome of death, MI and stroke occurred more frequently in the PCI group (CABG 18.7% vs. PCI 26.6%; $p = 0.005$). CABG also had significantly lower rates of mortality (CABG 10.9% vs. PCI 16.3%; $p = 0.049$) and MI (CABG 6.0% vs. PCI 6.0%; $p < 0.001$); however, there were more strokes in the surgical group (CABG 5.2% vs. PCI 2.4%; $p = 0.03$), mostly due to strokes that occurred within 30 days after the procedure. Interestingly, no interaction was observed with the SYNTAX score in the FREEDOM trial. Including the FREEDOM trial, there is compelling evidence from 13 trials and more than 4000 diabetic patients that CABG results in better survival compared with PCI.[13] In non-diabetic patients, however, there seems to be no difference in survival between CABG and PCI.

THE INFLUENCE OF TRIAL RESULTS ON CLINICAL PRACTICE

One of the main concerns of clinical trials is the potentially limited applicability of its results to everyday clinical practice. In general, randomized clinical trials are considered to provide the most unbiased and precise evidence for clinicians.[50] Blinding, randomization and other issues of internal validity receive much attention, but the external validity or generalizability determines what the usability of the results will be in clinical practice. There is a delicate balance between the need for exclusion criteria to optimize internal validity of efficacy and the need for less stringent criteria to determine an intervention's effectiveness for clinical practice. Elderly patients and patients with common concomitant medical conditions are frequently excluded,[51] whereas these patients reflect an important share of all patients that suffer from MVD.

In the early CABG versus PCI trials (Table 1), only 5–10% of all patients screened for participation were randomized,[14] thereby limiting the applicability of the results to everyday clinical practice. For instance, in the BARI trial, only 7% (1829 of 25,200) of all screened patients with MVD were eventually randomized.[52] The trial excluded patients above 80 years of age, which clearly limits the applicability of the results of the trial.

As noted earlier, the SYNTAX trial used an all-comer design to increase generalizability and determine the best treatment option in a real-world population.[53, 54] All patients with three-vessel and/or left main disease were discussed by the heart team. Inclusion was based on discussions between a cardiologist and cardiac surgeon, applying the limited number of exclusion criteria. When both agreed that the patient was equally eligible for CABG or PCI, the patient was randomized. If the patient was not randomized, he/she was still followed in the appropriate PCI or CABG registry. In total, 4337 patients were screened and discussed, of which 3075 (71%) were included in the study. Of these, 1800 patients were randomly assigned to undergo CABG (897 patients) or PCI (903 patients) and the remaining 1275 were followed in the registries.[32, 55] These data show that the trial indeed reflected a real-world population as much as possible, while also preserving internal validity. Therefore, the results of the SYNTAX trial are particularly well applicable to everyday clinical practice.

Large comparative effectiveness studies of registries are the only way to assess the generalizability of trial results in everyday clinical practice. There are two major comparative effectiveness studies that provide insights on revascularization in patients with MVD.[35, 36] While exclusions might limit the generalizability of randomized trials, comparative effectiveness suffer from selection bias. There are always specific factors why PCI or CABG is preferred. For instance, the patient's frailty or expected treatment adherence can play

Table 2. Economic Analyses of CABG versus PCI in MVD patients

Study	Follow-up, y	PCI using stent, %	Enrollment	CABG cost	PCI cost	Δ costs (CABG-PCI)	ICER	Conclusion
EAST[98]	3	0	1987-1990	25,310	23,734	1,576	NR	Early cost benefit of PCI is lost
EAST[97]	8	0	1987-1990	46,548	44,491	2,057	NR	Early cost benefit of PCI is lost
ERACI I[25]	1	0	1988-1990	12,938	6,952	5,986	NR	Costs higher with CABG
ERACI I[92]	3	0	1988-1990	13,000	7,524	5,476	NR	Costs higher with CABG
BARI[89]	5	0	1988-1991	58,889	56,225	2,664	26,117/LY [a]	CABG cost effective and better QoL
BARI[88]	12	0	1988-1991	123,000	120,750	2,250	14,300/LY [a]	CABG cost effective and better QoL
RITA[93]	2	0	1988-1991	£8,739	£6,916	£1,823	NR	Cost higher with CABG
RITA[87]	6.5	0	1988-1991	£9,268	£8,842	£426	NR	Early cost benefit of PCI is lost
MASS II[86]	1	68 (BMS)	1995-2000	14,095[b]	13,099[b]	996	NR	Costs were similar
MASS II[96]	5	68 (BMS)	1995-2000	24,614[b]	25,831[b]	−1,217	NR	CABG cost-effective
AWESOME[95]	5	54 (BMS)	1995-2000	100,522	81,790	18,732	PCI dominant	PCI economically dominant
ARTS I[94]	1	100 (BMS)	1997-1998	13,638	10,665	2,973	21,000/patient who survives event free	CABG cost-effective
ARTS I[90]	3	100 (BMS)	1997-1998	€16,100	€14,302	€1,798	€19,257/patient who survives event free	CABG is more costly, but also more effective. CABG seems economically attractive
SYNTAX[85]	1	100 (DES)	2005-2007	39,581	35,991	3,590	PCI dominant	PCI largely economically dominant, except for high complex patients
FREEDOM[91]	5, and lifetime projection	100 (DES)	2005-2010	114,571	109,179	5,392	8,132/QALY	Despite higher initial costs, CABG is highly cost-effective in diabetics

Costs are in US $, unless stated otherwise. [a] in favor of CABG. [b] reported as angina-free costs.

ARTS, Arterial Revascularization Therapies Study; AWESOME, Angina with Extremely Serious Operative Mortality Evaluation; BARI, Bypass Angioplasty Revascularization Investigation; CABG, coronary artery bypass grafting; EAST, Emory Angioplasty versus Surgery Trial; ERACI, Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; ICER, incremental cost-effectiveness ratio; MASS, Medicine, Angioplasty, or Surgery Study; MVD, multivessel disease ; NR, not reported; PCI, percutaneous coronary intervention; RITA, Randomized Intervention Treatment of Angina; SoS, Stent or Surgery; SYNTAX, SYNergery Between PCI With TAXUS and Cardiac Surgery; y, years

a role, but there might also be factors are difficult to capture and adjust in comparative analyses. Residual confounding is another issue in observational research, which may distort the validity of the results. Differences in age, comorbidities and the urgency of treatment can be controlled, but there might be factors that cannot be measured and adjusted. This could have had an influence on the survival difference between CABG and PCI in the two studies. The ASCERT study used sophisticated sensitivity analyses to show the potential impact and the authors acknowledge the potential impact of residual confounding.

The issues of external validity in randomized trials and the internal validity problems of comparative effectiveness research show that the two are complementary. The applicability of trials can be improved through less stringent exclusion criteria, whereas more accurate and elaborate registries will enhance the internal validity of comparative effectiveness studies.

Appropriateness of the Revascularization Method

The best treatment option in the individual patient is not always straightforward, since there are multiple factors that have to be taken into account and patients do not completely align with the guidelines. Therefore, the ACCF updated their appropriate use criteria (AUC), incorporating guidelines, trial evidence and expert opinion. The result is an appropriateness scale for a wide range of clinical scenarios. The selected treatment is deemed appropriate when the expected benefits exceeded the expected negative consequences of the treatment.[56]

The criteria provide a methodology to quantify the impact of trial evidence on everyday clinical practice. Large registries found rates of inappropriate revascularization procedures in both PCI (12–14%) and CABG (1–2%).[57-59] The rate of inappropriate revascularizations should not be expected to be zero, due to the exceptions that have not been captured in the predefined clinical scenarios. However, the evidence of inappropriate PCIs is increasing and several factors are likely to play a role. First, a patient's perceptions and the physician's guidance about the risks and benefits of PCI or CABG are likely to play a role. Patients may prefer the early and rapid recovery after PCI over the long-term survival benefits of CABG.[60] A second explanation is that the clinical decision pathway is more in favor of PCI than CABG; it is a small step to perform *ad hoc* stenting after initial diagnostic angiography. Another explanation is that some physicians believe that following guidelines does more harm than benefit to patients. A recent Medscape survey showed that 43% of 645 interviewed physicians believe that guidelines have a negative impact on patient care.[61]

There are some limitations to the AUC. First, there is only moderate concordance between a series of cardiologists and the AUC panel that developed the methodology.[62] In addition, this technical panel is relatively small (n = 17) and the number of clinical scenarios is limited. Despite the criticisms, the growth and increasing use of appropriateness criteria provide valuable information for improving the framework and underline that this methodology provides an important tool of measuring how evidence from trials, large registries and guidelines is integrated in clinical practice.[63]

Risk Scores

In clinical practice, the decision to revascularize depends on the expected risks and benefits of the treatment options. Risk models are important tools in these clinical considerations. For patients with coronary artery disease, there are several risk models available, which can be divided into clinical, anatomical and combined models.

Clinical risk models use patient characteristics, comorbidities, cardiac history, ejection fraction and the type of procedure to predict short-term mortality after the revascularization.[64-68] The original EuroSCORE overpredicts surgical mortality in contemporary datasets.[69, 70] The EuroSCORE II improved calibration in patients with a predicted mortality of <30%.[71, 72] The original EuroSCORE, however, has been shown to be a well-calibrated predictor of in-patient mortality in patients undergoing PCI,[73] thereby forming a useful tool for decision-making in patients with coronary artery disease. The STS score is widely used in the USA for predicting operative mortality (STS-PROM), as well as eight other outcomes, such as risk of prolonged length of stay, stroke and renal failure.[67] For patients undergoing PCI, the NCDR CathPCI risk score represents a contemporary and accurate risk prediction model with good calibration and discrimination.[74]

Anatomy-based scores focus on the anatomical complexity of the lesion for the prediction of mortality.[68, 75] The SYNTAX score takes into account anatomical characteristics of the lesion including bifurcations, total occlusions, thrombus, calcification and small vessels.[68] The score is a strong predictor of death and other adverse events during long-term follow-up for PCI, but is of less significance for CABG.[76] Hypothesis-generating subgroup analyses from the SYNTAX trial showed that there was a stepwise increase in events, according to SYNTAX score categories in the PCI cohort, while there was no predictive value of the score for the CABG group.[33]

Since clinical and anatomical variables are complementary, risk models implementing a combination of the two are expected to improve risk prediction. Several attempts to combine factors such as age, lung disease, renal function and other patient characteristics with the SYNTAX score have been undertaken.[77-82] The results of these initial studies are

promising and more validation studies are expected.[65] Recently, the SYNTAX score II was developed and subsequently validated in a large external registry.[79] The score consists of two angiographic (SYNTAX score and presence of left main disease) and six clinical variables (age, creatinine clearance, left ventricular ejection fraction, peripheral vascular disease, gender and chronic obstructive pulmonary disease). The new score can be used to better guide decision-making between CABG and PCI.

HEART TEAM

Despite the attempts to incorporate additional variables in the risk scores, there will always be factors that are not included but still need to be considered in the decision-making. Currently, factors that are not considered in risk scores consist of frailty, expected treatment adherence, hostile chest and BMI. Moreover, no single risk score can accurately predict outcome in the individual patient for which the treatment decision at hand has to be made. Therefore, risk scores should be considered a complement to clinical judgment.

These considerations should be done in a multidisciplinary heart team.[58] In the SYNTAX trial, this approach was used to decide whether patients were eligible for both CABG and PCI and could, thus, be randomized. The team consists of at least a clinical cardiologist, interventional cardiologist and cardiac surgeon, and is currently recommended by major cardiac associations.[9, 10] With the combination of all this expertise, the patient is more likely to undergo the treatment that is most beneficial for their specific situation.

In order to ensure implementation of the heart team, financial and clinical incentives should be aligned. Heart team meetings require time investment of medical specialists and therefore appropriate reimbursement is an important precondition. For instance, in the Netherlands, heart team discussions are reimbursed since payers recognize the long-term benefits of the appropriate revascularization method. Healthcare systems should carefully evaluate whether the short-term payer is the same as the payer for long-term costs.

HEALTH ECONOMICS OF REVASCULARIZATION

Approximately, 33% (84 million) of all American adults have some form of cardiovascular disease and of these, 15 million suffer from coronary heart disease.[83] The annual total costs of cardiovascular disease and stroke in the USA are approximately US$313 billion, representing 15% of the total healthcare expenditures.[83] For comparison, the

expenditure on cancer and benign neoplasms was US$228 billion in 2008. In the future, a rise in expenditure on coronary heart disease is projected (2020: US$470 billion; 2025: US$622 billion; 2030: US$818 billion). The expenditure on ischemic heart disease is expected to increase from US$47 billion in 2015 to US$106 billion in 2030. Modern societies are becoming increasingly more aware of this unsustainable growth of healthcare expenditures.[84]

Therefore, cost–effectiveness considerations become increasingly important. Several trials of MVD patients have published health economic analyses in addition to clinical outcomes (Table 1).[25, 85-98] With the exception of one study,[25, 92] all initial trials showed that the early cost benefit of balloon angioplasty compared with CABG was lost at long-term follow-up. The BARI trial showed that the incremental cost–effectiveness ratio for CABG was acceptable at 5 years (US$26,117/life year gained)[89] and even better at 12 years of follow-up (US$14,300/life year gained).[88] The RITA trial found higher costs with CABG at 2 years,[93] but this difference disappeared at long-term follow-up.[87]

The economic analyses of CABG versus BMS show conflicting results. The MASS II and ARTS found that CABG was cost effective, both at short and long-term follow-up.[86, 90, 94, 96] This means that CABG was more costly, but also more effective in improving clinical outcomes for patients with MVD. The AWESOME study, however, showed considerably lower costs (US$18,732) and better outcomes with PCI. Therefore, PCI was an economically dominant strategy.

The SYNTAX trial showed that PCI with DES was less costly, and more effective than CABG, leading to an economically dominant position of PCI at 1 year.[85] However, in patients with a more complex anatomy, PCI was increasingly expensive (US$43,486/quality-adjusted life year). The cost–effectiveness analysis of the FREEDOM trial was the most elaborate economic analysis in diabetic patients with MVD and combined 5-year trial data with lifetime projections.[91] The initial higher costs of CABG (Δ = US$8622), narrowed to a difference of US$3641 at 5 years, while gaining 0.03 quality-adjusted life years. Using lifetime projections, the incremental cost–effectiveness ratio of CABG versus DES was US$8132 per quality-adjusted life year gained. These results suggest that CABG is a more attractive treatment option than PCI, both clinically and economically.

Across all economic analyses, the more invasive CABG procedure and longer hospital stay contribute to the higher upfront costs with CABG compared with PCI. At longer follow-up, the higher rate of repeat revascularizations with PCI counterbalance this difference, leading to similar costs with CABG and PCI. Contemporary long-term clinical outcomes show that CABG is more effective. Combined with the similar long-term costs, it is expected

that CABG will be superior both clinically and economically. This hypothesis is to be tested in the upcoming 5-year cost–effectiveness analysis of the SYNTAX trial. Due to its contemporary all-comer design, its results are anticipated to give the final answer on the cost–effectiveness of CABG versus PCI in patients with left-main or MVD.

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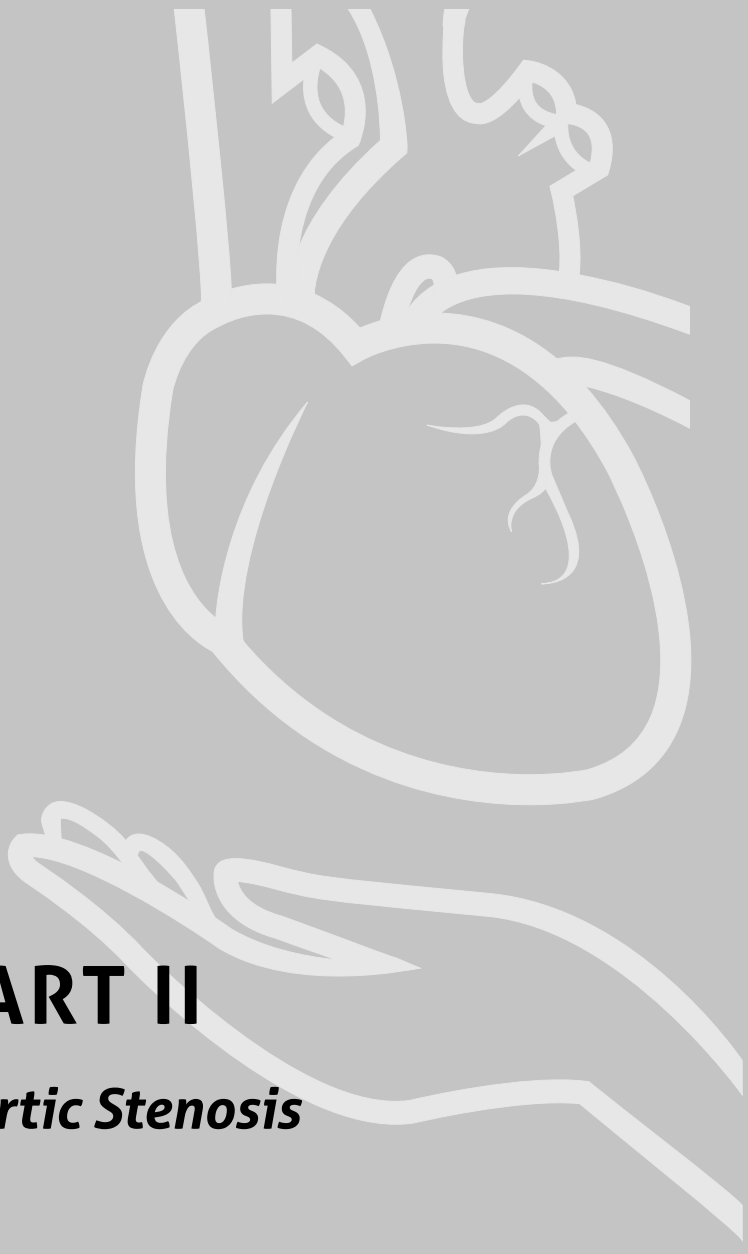

PART II

Aortic Stenosis

CHAPTER 4

Aortic Stenosis in the Elderly: Disease Prevalence and Number of Candidates for Transcatheter Aortic Valve Replacement: a Meta-Analysis and Modeling Study

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J Am Coll Cardiol. 2013;62:1002-12.

ABSTRACT

Objectives

The purpose of this study was to evaluate the prevalence of aortic stenosis (AS) in the elderly and to estimate the current and future number of candidates for transcatheter aortic valve replacement (TAVR).

Background

Severe AS is a major cause of morbidity and mortality in the elderly. A proportion of these patients is at high or prohibitive risk for surgical aortic valve replacement, and is now considered for TAVR.

Methods

A systematic search was conducted in multiple databases, and prevalence rates of patients (>75 years) were pooled. A model was based on a second systematic literature search of studies on decision-making in AS. Monte Carlo simulations were performed to estimate the number of TAVR candidates in 19 European countries and North America.

Results

Data from 7 studies (n = 9,723 subjects) were used. The pooled prevalence of all AS in the elderly was 12.4% (95% confidence interval [CI]: 6.6% to 18.2%), and the prevalence of severe AS was 3.4% (95% CI: 1.1% to 5.7%). Among elderly patients with severe AS, 75.6% (95% CI: 65.8% to 85.4%) were symptomatic, and 40.5% (95% CI: 35.8% to 45.1%) of these patients were not treated surgically. Of those, 40.3% (95% CI: 33.8% to 46.7%) received TAVR. Of the high-risk patients, 5.2% were TAVR candidates. Projections showed that there are approximately 189,836 (95% CI: 80,281 to 347,372) TAVR candidates in the European countries and 102,558 (95% CI: 43,612 to 187,002) in North America. Annually, there are 17,712 (95% CI: 7,590 to 32,691) new TAVR candidates in the European countries and 9,189 (95% CI: 3,898 to 16,682) in North America.

Conclusions

With a pooled prevalence of 3.4%, the burden of disease among the elderly due to severe AS is substantial. Under the current indications, approximately 290,000 elderly patients with severe AS are TAVR candidates. Nearly 27,000 patients become eligible for TAVR annually.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease in developed countries, and its impact on public health and health care resources is expected to increase due to aging Western populations.[1, 2] Each year, approximately 67,500 surgical aortic valve replacements (SAVR) are performed in the United States.[3] Studies describing the prevalence of AS are scarce and report disparate results (3% to 23%),[4, 5] and currently there is no systematic overview of population-based studies that have assessed the prevalence of AS.

The emergence of transcatheter aortic valve replacement (TAVR) has renewed interest in the epidemiology of AS. In particular, these data may be important to predict the number of TAVR candidates, service development, financial planning, and physician training. In addition, estimates of potential TAVR candidates at intermediate and low surgical risk are not available. Several factors must be considered when estimating the number of TAVR candidates: the percentage of patients with severe AS who are symptomatic; the proportion of patients with symptomatic severe AS who do not undergo SAVR and could thus be considered TAVR candidates; and the percentage of those patients referred for TAVR who actually receive a transcatheter valve.

Therefore, we sought to assess the prevalence of AS in the general elderly population (age ≥75 years) through a systematic review and meta-analysis of population-based studies. The second objective was to systematically estimate the number of elderly patients who are TAVR candidates in both the European countries and North America.

METHODS

Studies were identified through a systematic search of MEDLINE and EMBASE in February 2012. Keywords included "valvular heart disease," "heart valve disease," "aortic stenosis," "aortic valve stenosis," "epidemiology," "incidence," "prevalence," and "survey." No time restrictions were applied. Reference lists of selected studies and (systematic) reviews were examined, and the related article feature in PubMed was used to maximize relevant study identification.

All titles and abstracts were screened independently by two investigators using the following criteria: 1) the publication was an original full-length manuscript in a peer-reviewed journal; 2) the publication reported numbers of AS cases and sample size or the prevalence of AS in the general elderly population (≥75 years of age); and 3) AS

and AS severity was diagnosed with echocardiography.[6, 7] The definition of AS used in each study was extracted, as was other relevant information including study location, inclusion period, and patient characteristics. After excluding manuscripts on the basis of title and abstract, the remaining full-text manuscripts were carefully assessed and were evaluated according to the criteria. If overlap between studies existed, only the publication with the largest population was included. Disagreement on study inclusion was solved by consensus.

For each included study, the prevalence rate of AS and its 95% binomial confidence interval (CI) was calculated based on the numbers of subjects in the sample and the number of patients with AS. These rates were subsequently combined to produce a pooled prevalence rate of both AS and severe AS. Both fixed- and random-effects models were used, and results of the appropriate model are presented as Forest plots. The fixed-effects model was performed using the inverse variance method and the random-effects model with the DerSimonian and Laird method. Heterogeneity was assessed by the Cochran Q test and I^2 statistics, derived from the inverse variance fixed-effects model.[8] All analyses were performed with Stata SE version 12.0 (StataCorp, College Station, Texas).

Estimation of TAVR Candidates

To estimate the number of elderly patients who could potentially be treated with TAVR under current indications, we performed a second literature search on clinical decision-making in patients with severe AS. Specifically, we searched for studies that reported: 1) the percentage of patients with severe AS who experienced symptoms; 2) the percentage of patients with symptomatic severe AS who did not undergo SAVR and could thus be considered potential TAVR candidates; and/or 3) the percentage of those patients referred for TAVR who actually received a transcatheter valve. As TAVR is an approved therapy for patients at high operative risk, we also determined the proportion of elderly high-risk patients (The Society of Thoracic Surgery-Predicted Risk Of Mortality [STS-PROM] score ≥10%) undergoing SAVR,[9] and the percentage of patients who would be considered TAVR-eligible. In anticipation of current and potential future trials in lower risk groups, estimates of the proportion of intermediate- and low-risk patients were also derived. For all studies, the point estimate and 95% binomial CI were calculated.

These data were combined to produce a pooled percentage estimate for each individual search. In each case, a fixed- or random-effects model was used and heterogeneity was assessed. To calculate national estimates of the number of patients with AS and TAVR candidates, we obtained population demographic data focusing on the elderly (≥75 years of age) for the following nations: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, the Republic of Ireland, Luxembourg, Norway, Poland,

Portugal, Spain, Sweden, Switzerland, the Netherlands, the United Kingdom, Canada, and the United States.[10-12] The annual number of new TAVR candidates was calculated using the number of people ages 75 years old in 2011 in the individual countries.

A flowchart was built in TreeAge Pro 2011 (TreeAge Software, Williamstown, MA). The probabilities in the flowchart were based on the pooled estimates from the systematic literature searches. Beta distributions were used and 10,000 Monte Carlo simulations were performed to estimate the number of elderly patients who are eligible to undergo TAVR, along with its 95% percentile CI.

To account for the heterogeneous nature of the studies, sensitivity analyses were performed. In particular, the proportion of patients receiving TAVR after referral for TAVR assessment was determined using European studies alone and then by combining European and U.S. studies. This analysis was performed to account for the different adoption of TAVR in the United States, where until recently TAVR was only used in the context of clinical trials. In a second sensitivity analysis, we varied the percentage of high-risk SAVR-eligible patients who undergo TAVR.

RESULTS

The systematic literature search yielded 1,523 studies. After the title and abstract were screened, 1,408 studies were excluded because they did not focus on the epidemiology of disease. After assessing full-text articles, another 109 studies were excluded because they were not performed in the general elderly population, AS was not assessed, or because it was not an original publication. After the inclusion of an additional study through cross-referencing, our final analysis consisted of 7 studies, with a total of 9,723 elderly patients (Fig. 1).[1, 4, 5, 13-16] The characteristics of these studies are outlined in Table 1. The 7 studies reported the prevalence of AS in 9 study populations on 3 continents. The study periods ranged from 1989 to 2009. All studies had a cross-sectional character, and most were part of larger population-based cohort studies. In all 7 studies, echocardiography was used to diagnose AS, although definitions of AS and its severity were variable (Table 1).

The combined prevalence of AS in the elderly was reported in 6 studies and ranged from 2.6% to 22.8% (Fig. 2A).[4, 5, 13, 15, 16] The pooled prevalence was 12.4% (95% CI: 6.6% to 18.2%) using a random-effects model ($I^2 = 98.5\%$; $Q = 337.70$, $p < 0.001$). The prevalence of severe AS in the elderly was reported separately in 5 studies and ranged from 1.2% to 6.1% (Fig. 2B).[1, 4, 5, 13, 14, 16] The pooled prevalence of severe AS was 3.4% (95% CI: 1.1% to 5.7%) using a random-effects model ($I^2 = 85.7\%$; $Q = 27.99$, $p < 0.001$).

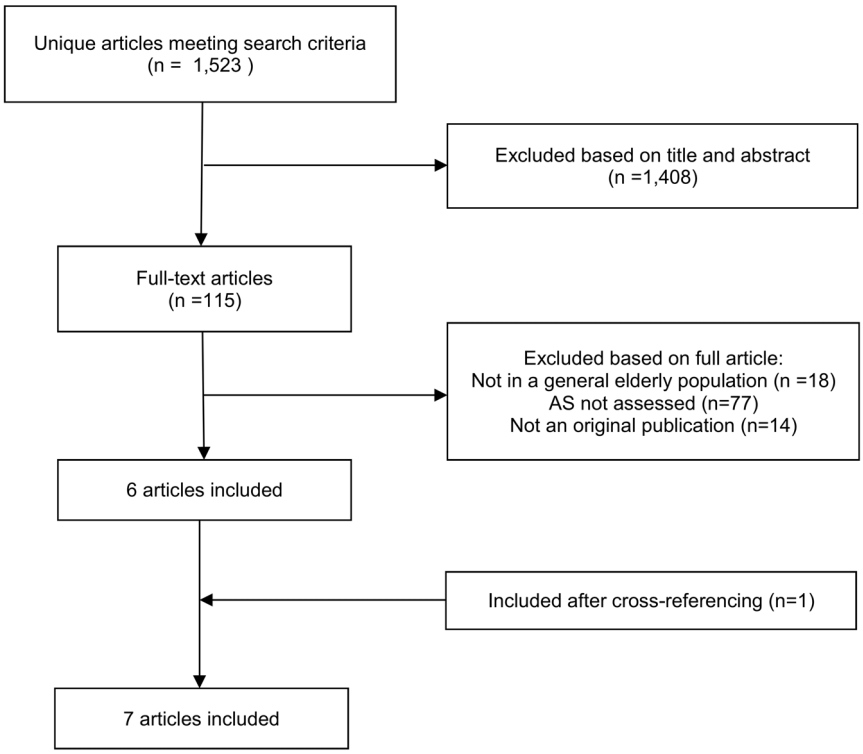


Figure 1. Flow Chart of Study Selection
AS, Aortic stenosis

These estimates of the prevalence of AS in patients ≥75 years old correspond to approximately 4.9 million elderly patients with AS in the European countries and 2.7 million in North America. If only symptomatic severe AS is considered, this translates to 1.0 million elderly patients in the European countries and 540,000 in North America. In 2011, 8.5% of the population in the 19 European countries was ≥75 years of age, and this number is expected to increase to 10.7% in 2025 and 16.6% in 2050.[11] In North America, similar increases in the population demographics of the elderly are expected (2025, 8.3%, and 2050, 11.8%).[10, 12] These numbers correspond to approximately 1.3 million and 2.1 million patients with symptomatic severe AS in the 19 European countries in 2025 and 2050, respectively. In North America, there will be an estimated 0.8 million and 1.4 million patients with symptomatic severe AS in 2025 and 2050, respectively.

Estimates of TAVR Candidates

The number of elderly patients who could potentially benefit from TAVR was estimated using the model outlined in Figure 3, with inputs from the systematic search and meta-analyses (Fig. 4). Seven studies reported the percentage of patients with severe AS who

Table 1. Main Study Characteristics of the Included Studies

Author, year, study, country	Study design Study period Population % men	Age (y) category in meta-analysis	Recruitment method Examination period	Response rate (%) and reasons for exclusion	Diagnostic method and definition of AS
Lorz (1993) Switzerland[15]	Cross-sectional study 70-96 y (n=129) 43% men	70-96, Mean 80 ± 6.6 (n=129)	Random selection within the community and nursing homes. 1990	51%; due to death, unable to contact, and "other reasons".	Doppler echo; All AS: Thickening of cusps, V_{max} >1.7m/s level, or systolic separation of cusps <15mm
Lindroos (1993) The Helsinki Ageing Study, Finland[14]	Cross sectional sub-study of larger population-based study >55 y (n=552) 28% men	75-86 (n=476)	Random selection in population register. 1990-1991	From the complete cohort 84 (9.3%) persons had died, 21 (2.3%) could not be contacted and 144 (16%) refused. 77% agreed with sub-study.	Doppler echo; Moderate AS:VR ≤0.35 and AVA 1.0-1.2 cm^2 Severe AS: VR ≤0.35 and AVA ≤1.0 cm^2 Critical AS: VR ≤0.35 and AVA ≤0.8 cm^2
Stewart (1997) Cardiovascular Health Study, USA[5]	Cross-sectional sub-study of larger population-based study >65 y (n=5,201) 43% men	>75 (n=1736)	Random selection from four communities of Medicare eligible patients. 1989-1990	57%; Reasons not stated. Also, subjects with AVR (n=23), MVS /MVR/both (n=37), BAV (n=4), AVE (n=2), or inadequate echo data (n=25) were excluded.	Doppler echo; All AS: thickened leaflets with reduced systolic opening and V_{max} >2.5 m/s
Lin (2005) Taiwan[13]	Cross-sectional analysis 20-97 y (n=3030) 59% of 2850 group were men	>80 (n=82)	Persons undergoing routine physical check-ups. Those with severe health conditions were excluded. Examination period NR	NR	Doppler echo; All AS: leaflet thickening with reduced systolic opening, gradient ≥20 mmHg Severe AS: gradient >50 mmHg

Table 1. Main Study haracteristics of the Included Studies (*continued*)

Author, year, study, country	Study design Study period Population % men	Age (y) category in meta-analysis	Recruitment method Examination period	Response rate (%) and reasons for exclusion	Diagnostic method and definition of AS
Nkomo (2006) * Olmsted county cohort USA[1]	Cross-sectional sub-study of larger community study >18 y old (n=16501) 49% men	>75 (n=6663)	Patients who underwent echocardiography in an affiliated hospital. 1990-2000	90% of the population received care at an affiliated hospital.	Doppler echo; Mild AS: V_{max} 2.5-3 m/s and AVA 1.5-2cm^2 Moderate AS: V_{max} 3-4 m/s and AVA 1-1.5 cm^2 Severe AS: V_{max}>4 m/s and AVA <1.0 cm^2
Van Bemmel (2010) Leiden 85-plus Study, the Netherlands[16]	Cross-sectional sub-study of larger population-based study >90 y (n=81) 33% men	>90 (n=81)	All inhabitants of Leiden > 85 y were invited. At 90 y participants were invited for echo examination. 1997-1999	13% of the total participants (n=705) refused to participate. 71% of the 277 participants eligible for echo were not able to visit the study center.	Doppler echo; Mild AS: gradient < 25 mmHg Moderate AS: gradient 25 - 40 mmHg Severe AS: gradient > 40 mmHg
Vaes (2012) BELFRAIL (BF_{C80+}) study, Belgium[4]	Cross-sectional analysis of population-based study >80 y (n=556) 37% men	>80 (n=556)	29 general practitioners in three regions included > 80 y olds. 2008-2009	Severe dementia and medical emergency patients were excluded.	Doppler echo; Mild AS: AVA >1.5 cm^2 Moderate AS: AVA 1.0 cm^2 - 1.5 cm^2 Severe AS: AVA <1 cm^2

AS, Aortic stenosis; AVA, aortic valve area; AVE, aortic valve endocarditis; AVR, aortic valve replacement; echo, echocardiography; MVS, Mitral valve stenosis; MVR, mitral valve replacement; VR, velocity ratio; V_{max}, peak velocity; NR, not reported

* only the Olmsted County community study was included in this analysis.[1] Of the three pooled population based studies in this publication, only the Cardiovascular Health Study was eligible and is included in this systematic review (Stewart et al. 1997)[5]. The other two studies did not meet the selection criteria, since the population studied was too young.

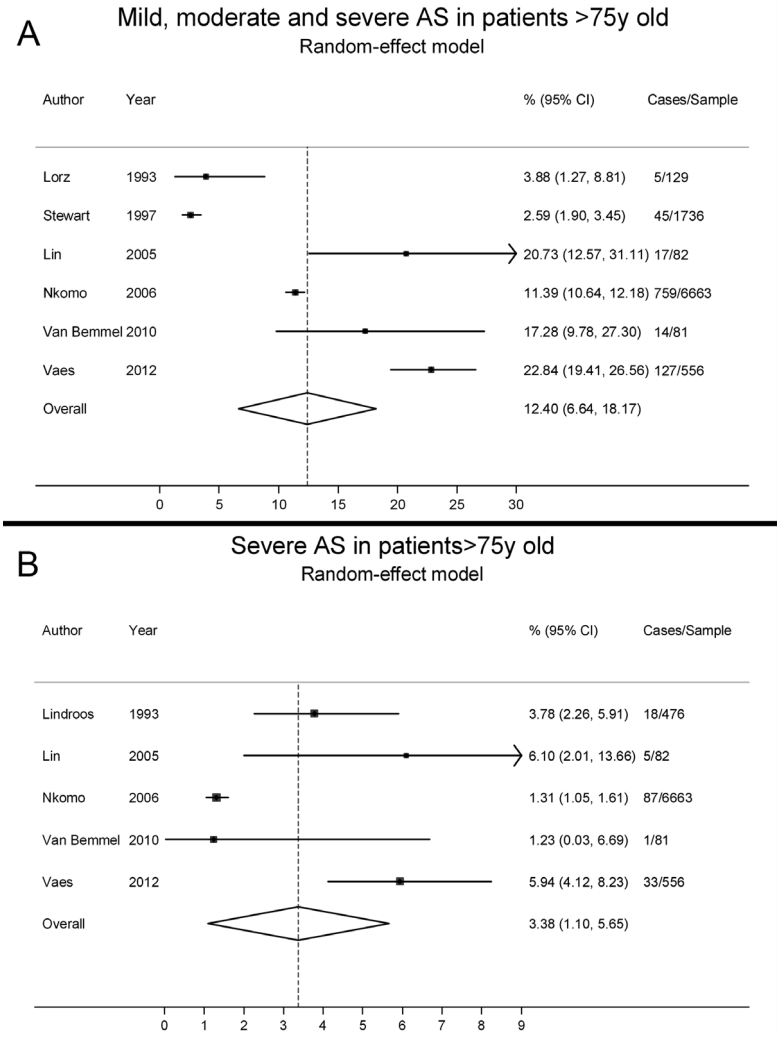


Figure 2. Forest Plots on the Prevalence of AS

2A. Mild, moderate and severe AS in the elderly, using a random-effect model. I^2=97.1%; Q=140.25, p<0.001.

2B. Severe AS in the elderly, using a random-effect model. I^2=85.7%, Q=27.99, p<0.001.

AS, Aortic stenosis.

were symptomatic, resulting in a pooled estimate of severe symptomatic AS of 75.6% (95% CI: 65.8% to 85.4%) (Fig. 4A, Supplementary Table 1). Of these patients with symptomatic severe AS, 40.5% (95% CI: 35.8% to 45.1%) did not undergo SAVR and thus could be considered candidates for TAVR (Fig. 4B, Supplementary Table 2). Nine studies reported the percentage of patients referred for TAVR who actually received a transcatheter valve (Supplementary Table 3). Three of these studies were performed in

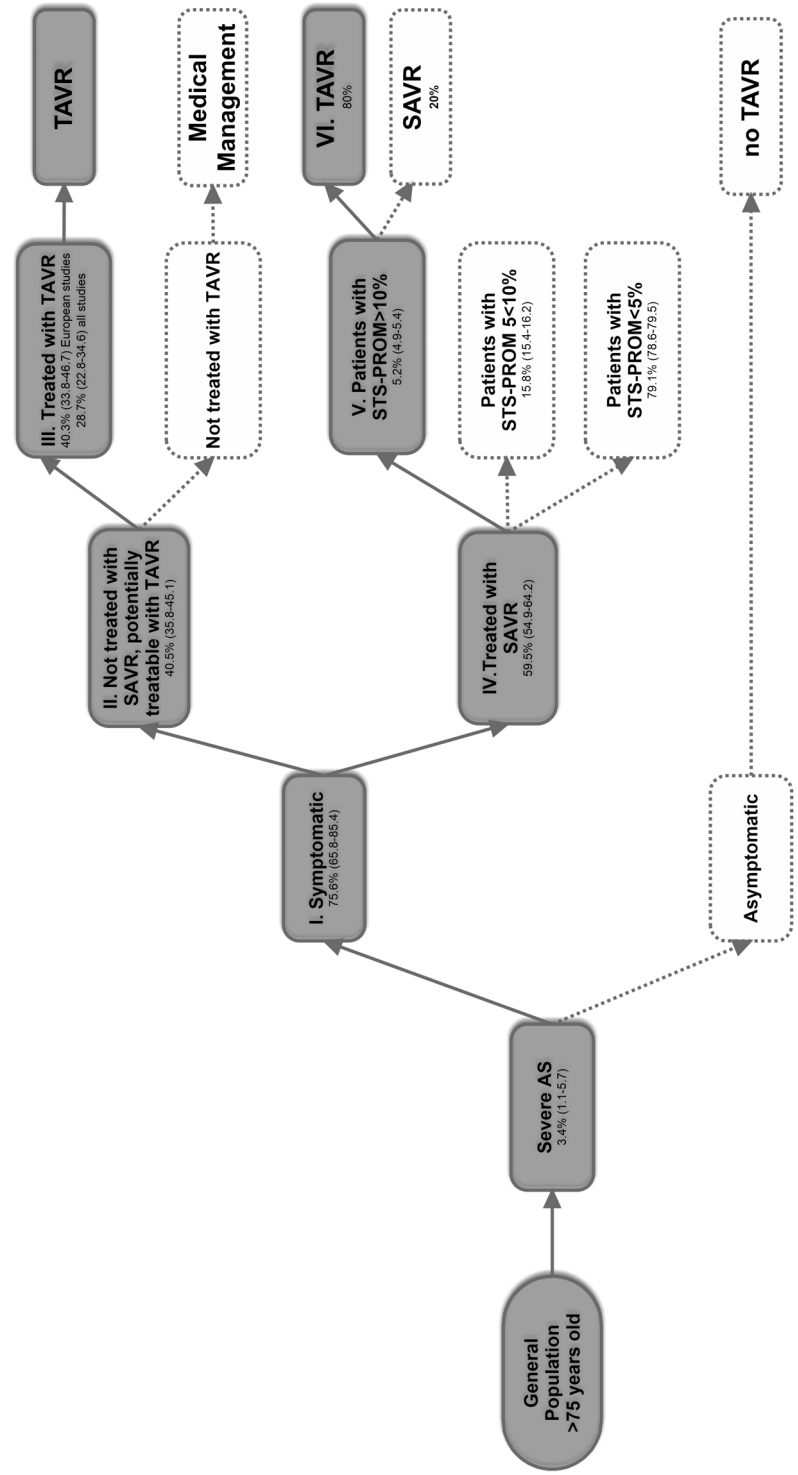


Figure 3. Model for the Estimation of TAVI Candidates in the Elderly
AS, Aortic stenosis; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgery-Predicted Risk of Mortality; TAVR transcatheter aortic valve replacement

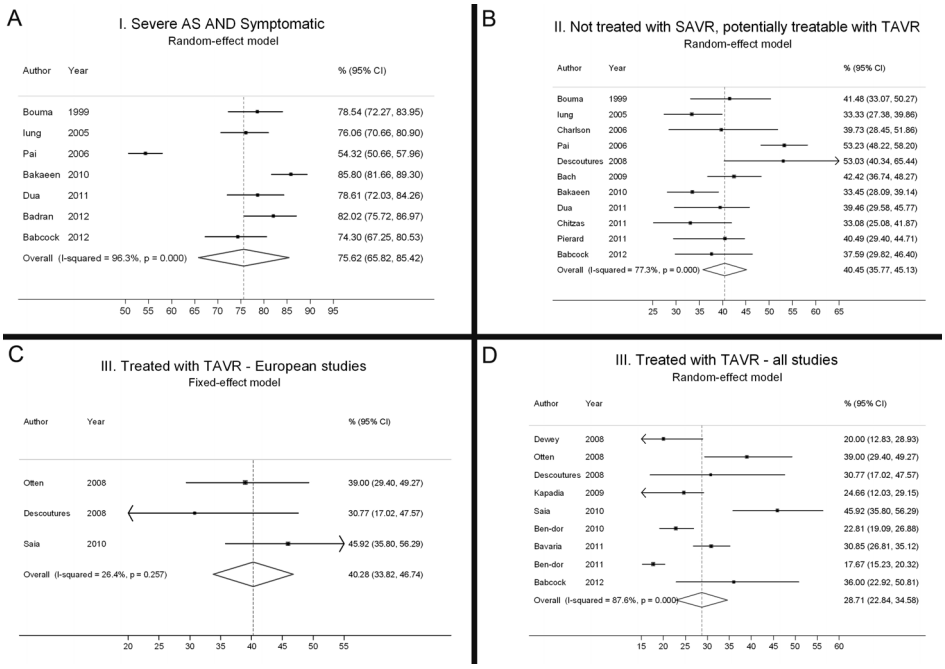
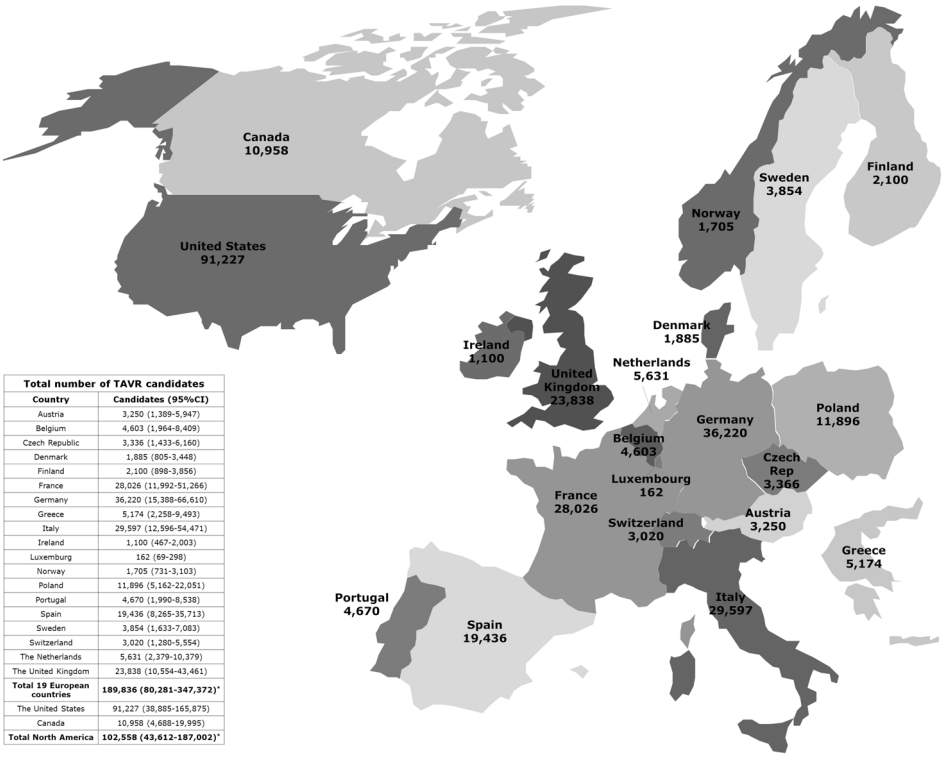


Figure 4. Forrest Plots of the Different Steps in the Estimation Model

Europe, and 6 in the United States. The pooled percentage including both European and U.S. studies was 28.7% (95% CI: 22.8% to 34.6%) (Figs. 4C and 4D, respectively). The European pooled percentage was 40.3% (95% CI: 33.8% to 46.7%), whereas the U.S. pooled percentage was 24.4% (95% CI: 18.9% to 29.8%). In total, 12.3% of patients with symptomatic severe AS at prohibitive surgical risk are TAVR candidates.

To assess the proportion of elderly SAVR patients who was deemed to be at high surgical risk, we used a study that reported on all elderly SAVR patients in the United States between 1999 and 2007.[17] Among elderly patients undergoing isolated SAVR, 5.2% (95% CI: 4.9% to 5.4%) were at high risk (STS-PROM ≥10%), 15.8% (95% CI: 15.4% to 16.2%) at intermediate risk (STS-PROM 5% to 10%), and 79.1% (95% CI: 78.6% to 79.5%) at low risk (STS-PROM <5%). A recent study showed that in a group of operable patients with a EuroSCORE (European System for Cardiac Operative Risk Evaluation) ≥15, approximately 80% were treated with TAVR.[18]

In 2011, there were 39,316,978 people ≥75 years of age in the European countries and 21,182,683 in North America.[10-12] Combining these figures with the Monte Carlo simulations in the model (Fig. 3), we estimated that a total of 292,000 high- or prohibitive-risk elderly patients with symptomatic severe AS are candidates for TAVR. Specifically, there



Total number of TAVR candidates	
Country	**Candidates (95%CI)**
Austria	3,250 (1,389-5,947)
Belgium	4,603 (1,964-8,409)
Czech Republic	3,336 (1,433-6,160)
Denmark	1,885 (805-3,448)
Finland	2,100 (898-3,856)
France	28,026 (11,992-51,266)
Germany	36,220 (15,388-66,610)
Greece	5,174 (2,258-9,493)
Italy	29,597 (12,596-54,471)
Ireland	1,100 (467-2,003)
Luxemburg	162 (69-298)
Norway	1,705 (731-3,103)
Poland	11,896 (5,162-22,051)
Portugal	4,670 (1,990-8,538)
Spain	19,436 (8,265-35,713)
Sweden	3,854 (1,633-7,083)
Switzerland	3,020 (1,280-5,554)
The Netherlands	5,631 (2,379-10,379)
The United Kingdom	23,838 (10,554-43,461)
Total 19 European countries	**189,836 (80,281-347,372)***
The United States	91,227 (38,885-165,875)
Canada	10,958 (4,688-19,995)
Total North America	**102,558 (43,612-187,002)***

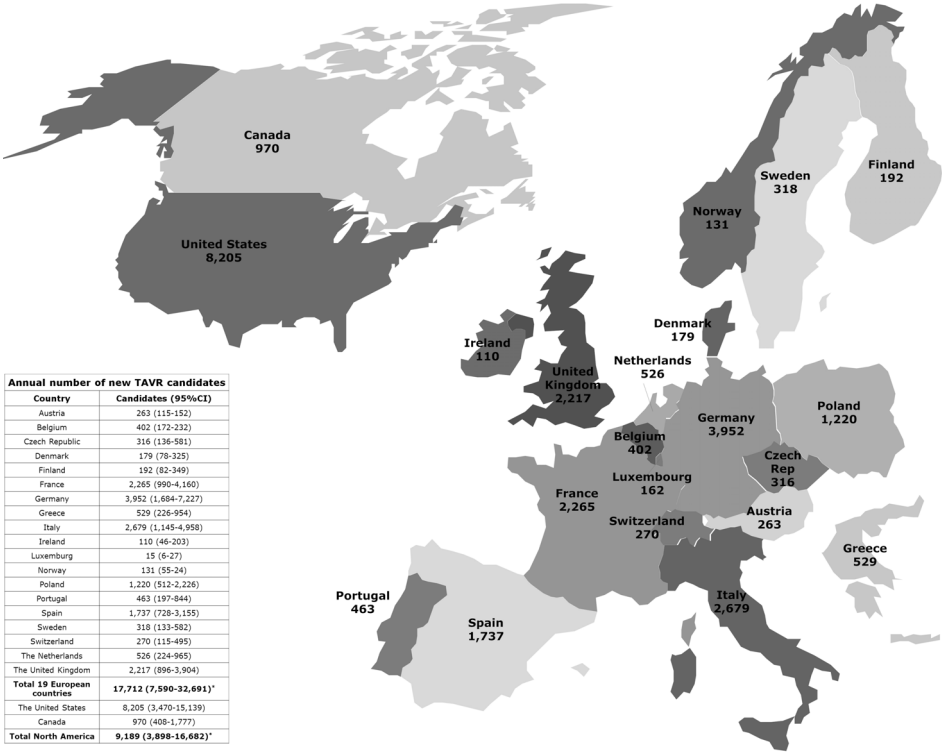
Figure 5. Total of TAVR Candidates in the Different Countries under the Current Treatment Indications

are 189,836 (95% CI: 80,281 to 347,372) TAVR candidates in the European countries and 102,558 (95% CI: 43,612 to 187,002) in North America. Annually there are 17,712 (95% CI: 7,590 to 32,691) new TAVR candidates in the European countries and 9,189 (95% CI: 3,898 to 16,682) in North America. The total and annual number of TAVR candidates in the individual countries is presented in Figures 5 and 6, respectively.

The intermediate surgical risk group comprises approximately 145,000 elderly patients with symptomatic severe AS. Specifically, there are 94,730 (95% CI: 40,574 to 171,896) patients at intermediate risk in the European countries and 50,733 (95% CI: 22,148 to 90,451) in North America. The low surgical risk group includes approximately 730,000 patients with symptomatic severe AS. Specifically, there are 477,314 (95% CI: 206,798 to 862,958) patients at low-risk in the European countries and 255,727 (95% CI: 108,549 to 460,026) in North America.

Sensitivity Analyses

In the pre-specified sensitivity analysis that varied the proportion of patients receiving TAVR after referral for TAVR assessment according to study location (28.7%, 95% CI:



Annual number of new TAVR candidates	
Country	**Candidates (95%CI)**
Austria	263 (115-152)
Belgium	402 (172-232)
Czech Republic	316 (136-581)
Denmark	179 (78-325)
Finland	192 (82-349)
France	2,265 (990-4,160)
Germany	3,952 (1,684-7,227)
Greece	529 (226-954)
Italy	2,679 (1,145-4,958)
Ireland	110 (46-203)
Luxemburg	15 (6-27)
Norway	131 (55-24)
Poland	1,220 (512-2,226)
Portugal	463 (197-844)
Spain	1,737 (728-3,155)
Sweden	318 (133-582)
Switzerland	270 (115-495)
The Netherlands	526 (224-965)
The United Kingdom	2,217 (896-3,904)
Total 19 European countries	**17,712 (7,590-32,691)***
The United States	8,205 (3,470-15,139)
Canada	970 (408-1,777)
Total North America	**9,189 (3,898-16,682)***

Figure 6. Annual Number of TAVR Candidates in the Different Countries under the Current Treatment Indications

22.8% to 34.6% in Europe and the United States combined), we estimated that approximately 220,000 patients are TAVR candidates. Of these, 142,658 (95% CI: 61,065 to 263,795) candidates lived in the European countries and 76,962 (95% CI: 32,805 to 140,673) in North America.

In the sensitivity analysis varying the percentage of high-risk operable patients who would undergo TAVR, the total number of TAVR candidates was 277,570 (95% CI: 119,406 to 512,707) assuming that 50% would undergo TAVR whereas there were 302,865 (95% CI: 129,433 to 550,562) candidates if all the high-risk patients would undergo TAVR. Finally, we estimated that the total number of patients with symptomatic severe AS in the intermediate-risk category was 145,936 (95% CI: 62,802 to 263,340), and 733,861 (95% CI: 310,623 to 1,302,586) in the low-risk category.

DISCUSSION

The current study found that the prevalence of AS in the elderly (≥75 years of age) is 12.4%, and severe AS is present in 3.4%. Among elderly patients with severe AS, 75.6% are symptomatic, and 40.5% of these patients are not treated surgically. From those, 40.3% are potentially treated with TAVR. In total, 12.3% of the prohibitive risk group are TAVR candidates. Among patients undergoing SAVR for severe symptomatic AS, 5.2% are high risk and 80% of those are potential TAVR candidates. Based on these data, we estimated that there are currently approximately 190,000 and 100,000 TAVR candidates in the European countries and North America, respectively. Each year, approximately 18,000 new TAVR candidates emerge in the European countries and 9,000 in North America.

The Prevalence of AS

Our estimates of the prevalence demonstrate that the overall burden of disease due to AS in the general elderly population is substantial. Population demographics clearly show that Western populations are aging, thereby further increasing the impact of AS. No effective medical therapy is available for patients with AS, and if not treated by intervention, the estimated 5-year survival of severe AS is only 15% to 50%.[7] These data suggest that the treatment of AS in the elderly will have an increasing impact on public health and health care resource consumption in the future.

Based on echocardiographic diagnosis, we found that severe AS occurs in 12.4% of the general elderly (≥75 years of age) population. Previous autopsy series and a study based on aortic valve diagnoses in Medicare claims have reported AS prevalence estimates of 9.2% and 16%, respectively.[19, 20] Our pooled prevalence of AS (12.4%) is lower than the estimates from Medicare claims, but covered a lower age group and did not include diagnoses of aortic regurgitation. The methodological differences between studies are likely to account for the variability in AS estimates.

We explored heterogeneity by assessing the individual study characteristics, but the limited number of studies prevented separate analyses. The heterogeneity is reflective of different diagnostic definitions for AS, dissimilar recruitment methods, and varying study periods (Table 1). Study participation was only 50% to 60% in 2 studies, making their results vulnerable for selection bias.[5, 15] In 1 study, AS was diagnosed using clinically indicated echocardiography.[1] That might have caused a lower prevalence rate of AS. Moreover, improvements of echocardiographic techniques and interobserver variability might have had an influence on the prevalence rates and heterogeneity.

The Number TAVR Candidates

Nearly 40.5% of all patients with symptomatic severe AS did not undergo SAVR (Fig. 4B). Possible explanations for the lower than expected rates of SAVR include excessive operative risk, advanced age, comorbidities, and patient preference.[21, 22] TAVR is a safe, effective, and less invasive treatment strategy for a highly selected proportion of the patients who do not undergo SAVR,[23] represented by the 40.3% of patients who underwent TAVR (Fig. 4C). The treatment decisions reflect heart team discussions, in which (interventional) cardiologists and cardiac surgeons combine risk models with additional factors such as frailty, porcelain aorta, and vessel tortuosity.[24]

The estimated large number of TAVR candidates has clinical, economic, and social implications. If the index admission costs (US $72,000) of the PARTNER (Placement of Aortic Transcatheter Valves) trial are applied,[25] treating all TAVR candidates would represent a budget impact of $13.7 billion in the European countries and $7.2 in North America. At a price of $30,000, the total device turnover would be approximately $8.7 billion. Although TAVR is cost effective in the United States for patients at high and prohibitive risk,[25, 26] data from other countries show that, for intermediate-risk patients, the costs of TAVR at 1 year are considerably higher than the costs of SAVR.[27] Importantly, cost is not the only factor that determines the adoption of novel technologies such as TAVR.[28] Reimbursement strategies, physician training, and health care culture may be related to the dissemination of this costly technology.

Despite budgetary concerns, current clinical trials are evaluating TAVR for patients at intermediate surgical risk (NCT01314313 and NCT01586910).[9, 29] If TAVR proves to be noninferior to SAVR in this population, we estimate that a further 145,000 patients would become TAVR eligible. Indeed, there is some evidence that suggests that TAVR is already being performed in these intermediate-risk patients.[18, 30] Thus, our estimates of the impact of positive outcomes in the ongoing trials are likely to be conservative. In the future, TAVR may even compete with SAVR in patients at low surgical risk,[30, 31] a group that comprises 730,000 severe AS patients in the European countries and North America combined.

TAVR learning curve analyses show increasing proficiency with evidence of plateau after the first 30 cases.[32] In addition, governmental bodies mandate that each TAVR center performs at least 20 to 50 TAVR procedures per year.[33-35] These requirements, combined with the figures from this study, are useful to estimate the number of TAVR centers and physicians who need to be trained in TAVR in the individual countries. For example, the 526 (95% CI: 224 to 965) new TAVR candidates per year in the Netherlands justify approximately 10 certified centers, assuming that each center performs 50 cases annually.

Similarly, the 8,205 (95% CI: 3,470 to 15,139) new TAVR candidates per year in the United States suggest a requirement of approximately 165 certified TAVR centers.

The divergent standards of medical evidence required to introduce new therapies in Europe and the United States are likely to account for the difference in TAVR dissemination between the continents.[36] Although the Edwards Sapien valve (Edwards Lifesciences, Inc., Irvine, CA) and Medtronic CoreValve (Medtronic, Inc., Minneapolis, MN) both received the Conformité Européenne (CE) mark in 2007, the U.S. Food and Drug Administration used trial data to approve the Edwards Sapien valve for patients at prohibitive and high surgical risk only in November 2011 and October 2012, respectively. Consequently, TAVR has been performed with greater frequency and for a wider range of indications in Europe than in the United States. The studies on decision-making in patients with AS reflect the commercial use of TAVR in Europe, whereas the U.S. studies display decision-making in a time when TAVR use was restricted to clinical trials. These differences in practice are likely to disappear after the commercialization of TAVR in the United States and were taken into account in our sensitivity analyses.

Study Limitations

Although we systematically searched the literature, relatively few reports on the prevalence of AS in the general population were identified. Additional population-based studies that use a unified echocardiographic definition of AS are warranted. The current study, however, reflects all of the currently available evidence on the prevalence of AS.

The estimation of TAVR candidates is as accurate as the currently available inputs and assumptions from the literature. However, we used sensitivity analyses to assess the influence of uncertain parameters. In addition, we included measures of uncertainty in each step of the model to calculate confidence intervals, representing the likelihood of the final estimates.

Conclusions

This systematic review and meta-analysis of population-based studies found that the prevalence of AS and severe AS among the elderly is 12.4%, and 3.4%, respectively. The overall burden of disease due to severe AS in the general elderly population is substantial. Our model showed that under the current indications approximately 290,000 elderly patients at high or prohibitive surgical risk could potentially be treated with TAVR in Europe and North America, and that each year there are approximately 27,000 new TAVR candidates. These estimates have considerable clinical, economic, and social implications.

ACKNOWLEDGMENTS

The authors would like to acknowledge the suggestions by Rachele Busca, MS, PharmD, and Liesl C. Birinyi-Strachan, BS, PhD, from Medtronic.

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APPENDIX

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Supplementary Table 1. Studies on the Percentage of Severe AS Patients Experiencing Symptoms

I. Severe AS and symptomatic							
Author	**Year**	**Study Design**	**Population**	**Definition severe AS**	**Symptoms linked to severe AS**	**Numerator**	**Denominator**
Bouma 1999[1]	1991-1993	Prospective registry, 205 patients; 3 academic centers, the Netherlands	Median 78 years 36% male	AVA≤1.0 cm^2 or gradient ≥50 mmHg	Asymptomatic: no angina or dyspnea (NYHA I)	205 - 44 asymptomatic= **161** symptomatic severe AS	**205** severe AS
Iung 2005[2]	2001	Prospective registry 5001 VHD patients; 92 centers, 25 European countries	Mean 80 years 47% male	AVA≤0.6 cm^2/m^2 of BSA and/ or gradient ≥50 mmHg	Asymptomatic: NYHA I or II and no angina	**216** symptomatic severe AS	**284** severe AS
Pai 2006[3]	1993-2003	Retrospective database 740 patients; 1 academic center, Loma Linda CA, US	Mean 71 years 51% male	AVA≤0.8 cm^2	exertional angina, shortness of breath, or syncope	740 – 338 asymptomatic = **402** symptomatic severe AS	**740** severe AS
Bakaeen 2010[4]	1997-2008	Retrospective database 345 patients; 1 VA center, Houston TX, US	Mean 73 years Gender NR	AVA≤1.0 cm^2	NR	71% of 140 medically treated and 96% of 205 SAVR treated are symptomatic→**296** symptomatic severe AS	**345** severe AS
Dua 2011[5]	2006-2008	Retrospective database 187 patients; 1 academic center, Loma Linda CA, US	Mean 74 years 56% male	AVA≤1.0 cm^2	exertional angina, syncope, presyncope, heart failure symptoms	**147** symptomatic severe AS	**187** severe AS
Badran 2012[6]	2008-2010	Retrospective database 178 patients; 1 academic center, Southampton, UK	Mean 79 years 48% male	AVA≤1.0 cm^2, gradient ≥40 mmHg, or 'visually severe'	Dyspnea, syncope, angina	**146** symptomatic severe AS	**178** severe AS
Babcock 2012[7]	2008-2010	Retrospective database 833 patients; 1 academic center, Jacksonville FL, US	Mean 73 years 52 % male	Moderate/severe AS, at least one: AVA<1.0 cm^2, gradient >40 mmHg, Vmax>4m/s, or "dimensionless index ≤0.25)	One of: Angina, syncope or dyspnea consistent with NYHA II	**133** symptomatic moderate/ severe AS	**179** severe AS

AS, aortic stenosis; AVA, aortic valve area; BSA, body surface area; echo, echocardiography; NR, not reported; NYHA, New York Heart Association; US, United States, UK, United Kingdom; VA, Veterans Affairs; VHD, valvular heart disease; V_{max}, peak velocity

Supplementary Table 2. Studies on the Percentage of Symptomatic Severe AS Patients who did not undergo SAVR and are Potential TAVR Candidates

II. Not treated with SAVR, potentially treatable with TAVR							
Author	**Years**	**Study Design**	**Population**	**Definition severe AS**	**Symptoms linked to severe AS**	**Numerator**	**Denominator**
Bouma 1999[1]	1991-1993	Prospective registry, 205 patients; Three academic centers, the Netherlands	Median 78 years 36% male	AVA≤1.0 cm^2 or gradient ≥50 mmHg	Asymptomatic: no angina or dyspnea (NYHA I)	135-79=**56** not treated with SAVR	**135** symptomatic severe AS
Iung 2005[2]	2001	Prospective registry 5001 VHD patients; 92 centers, 25 European countries	Mean 80 years 47% male	AVA≤0.6 cm^2/m^2 of BSA and/or gradient ≥50 mmHg	Asymptomatic: NYHA I or II and no angina	**72** not treated with SAVR	**216** symptomatic severe AS
Charlson 2006[8]	1995-1997	Retrospective database 124 patients; Two academic centers, US	Mean 81 years 35% male	AVA≤0.8 cm^2 or gradient ≥50 mmHg	Angina, CHF, dyspnea, syncope, fatigue, exercise intolerance	**29** not treated with SAVR	**73** symptomatic severe AS above 80 year
Pai 2006[3]	1993-2003	Retrospective database 740 patients; one academic center, Loma Linda CA, US	Mean 71 years 51% male	AVA≤0.8 cm^2	Exertional angina, shortness of breath, or syncope	402-188=**214** not treated with SAVR	**402** symptomatic severe AS
Descoutures 2008[9]	2006-2007	Prospective registry 66 patients; one academic center, Paris, France	Mean 83 years 58% male	AVA≤0.7 cm^2	NR	66-31=**35** not treated with SAVR	**66** symptomatic severe AS
Bach 2009[10]	2005	Retrospective database 369 patients; Three (VA, academic, private) centers, US	Mean NR# % male NR#	AVA≤0.9 cm^2, gradient ≥40 mmHg, or "clinical impression consistent with severe AS"	Angina, syncope, (pre)syncope, dyspnea, heart failure symptoms	**126** not treated with SAVR	**297** symptomatic severe AS ***
Bakaeen 2010[4]	1997-2008	Retrospective database 345 patients; One VA center, Houston TX, US	Mean 73 years Gender NR	AVA≤1.0 cm^2	NR	71% of non-SAVR group was symptomatic: 0.71*140=**99**	**296** symptomatic severe AS
Dua 2011[5]	2006-2008	Retrospective database 187 patients; One academic center, Loma Linda CA, US	Mean 74 years 56% male	AVA≤1.0 cm^2	Exertional angina, (pre)syncope, heart failure symptoms	71% of non-SAVR group was symptomatic: 0.71*81=**58**	**147** symptomatic severe AS

Supplementary Table 2. Studies on the Percentage of Symptomatic Severe AS Patients who did not undergo SAVR and are Potential TAVR Candidates (*continued*)

II. Not treated with SAVR, potentially treatable with TAVR							
Author	**Years**	**Study Design**	**Population**	**Definition severe AS**	**Symptoms linked to severe AS**	**Numerator**	**Denominator**
Chitzas 2011[11]	2000-2007	Retrospective database 132 patients; One VA center, San Francisco CA, US	Mean 73 years 100% male	AVA≤1.0 cm^2 or gradient ≥40 mmHg	Angina, dyspnea on exertion, shortness of breath, syncope	77% of non-SAVR group was symptomatic: 0.77*56=**43**	**130** symptomatic severe AS***
Pierard 2011[12]	2000-2007	Prospective registry 192 patients; One academic center, Brussels, Belgium	Mean 83 years 44% male	AVA≤1.0 cm^2 and gradient ≥30 mmHg	Angina, NYHA III/IV, syncope	**66** not treated with SAVR	**163** symptomatic severe AS
Babcock 2012[7]	2008-2010	Retrospective database 833 AS patients; One academic center, Jacksonville FL, US	Mean 73 years 52 % male	Moderate/severe AS, at least one of: AVA<1.0 cm^2, gradient >40 mmHg, Vmax>4m/s, or "dimensionless index ≤0.25)	One of: Angina, syncope or dyspnea consistent with NYHA II	**50** not treated with SAVR	**133** symptomatic moderate/severe AS

*** based on Dua et al. and Bakaeen et al. we assumed that 4% of the SAVR patients was asymptomatic

the total unoperated group (191) had a mean age of 73 year and 62% were males

AS, aortic stenosis; AVA, aortic valve area; BSA, body surface area; CHF, congestive heart failure; NR, not reported; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; US, United States, UK, United Kingdom; VA, Veterans Affairs; VHD, valvular heart disease; echo, echocardiography; V_{max}, peak velocity

Supplementary Table 3. Studies on the Percentage of Potential TAVR Candidates that received TAVR

III. treated with TAVR							
Author	**Years**	**Study Design**	**Population**	**Definition severe AS**	**Symptoms linked to severe AS**	**Numerator**	**Denominator**
Dewey[13] 2008	2005-2007	Prospective registry "Compassionate use or meeting current trial inclusion criteria" 105 patients One academic center, Dallas TX, US	Mean 80 years 48% male	AVA<1.0 cm^2 and Vmax>3.5m/s	NR	**21** underwent TAVR	**105** referred for TAVR
Otten 2008[14]	2005-2007	Prospective registry 100 patients One academic center, Rotterdam, the Netherlands	Mean 82 years 43% male	NR	NR	**39** underwent TAVR	**100** referred for TAVR
Descoutures 2008[9]	2006-2007	Prospective registry 66 patients; one academic center, Paris, France	Mean 83 years 58% male	AVA≤0.7 cm^2	NR	**12** underwent TAVR	**39** with a EuroSCORE≥20 were assessed for TAVR
Kapadia 2009[15]	2006-2007	Prospective registry "REVIVAL trial inclusion criteria" (inoperable and STS-PROM>15) 92 patients One academic center, Cleveland OH, US	Mean 81 years 55% male	NR	NR	**18** underwent TAVR	**92** referred for TAVR
Saia 2010[16]	2007-2008	Prospective registry 98 patients One academic center, Bologna, Italy	Mean 82 years 40% male	AVA≤0.75 cm^2 and AVA≤0.4 cm^2/m^2 of BSA	Angina (CCS ≥3), syncope, dyspnea (NYHA III/IV)	**45** underwent TAVR	**98** referred for TAVR
Ben-Dor 2010[17]	2007-2009	Prospective registry Screening for trial 469 patients One academic center, Washington DC, US	Mean 81 years 46% male	AVA<0.8 cm^2	NR	**107** were enrolled in TAVR trial	**469** were screened for TAVR trial

Supplementary Table 3. Studies on the Percentage of Potential TAVR Candidates that received TAVR (*continued*)

III. treated with TAVR							
Author	**Years**	**Study Design**	**Population**	**Definition severe AS**	**Symptoms linked to severe AS**	**Numerator**	**Denominator**
Bavaria 2011[18]	2007-2010	Prospective registry Screening for trial 681 patients One academic center, Philadelphia PA, US	NR	AVA<0.8 cm^2	NR	**153** were enrolled in TAVR trial	**496** (153+343) screened for TAVR trial
Ben-Dor 2011[19]	2007-2011	Prospective registry Screening for trial, but also continued access 900 patients One academic center, Washington DC, US	Mean 82 years 45% male	AVA<1.0 cm^2, or gradient >40 mmHg	NR	**159** underwent TAVR	**900** screened for TAVR trial
Babcock 2012[7]	2008-2010	Retrospective database; fitting the PARTNER trial criteria 833 AS patients; One academic center, Jacksonville FL, US	Mean 73 years 52 % male	Moderate/severe AS, at least one of: AVA<1.0 cm^2, gradient >40 mmHg, Vmax>4m/s, or "dimensionless index ≤0.25)	One of: Angina, syncope or dyspnea consistent with NYHA II	**18** TAVR candidates	**50** screened according to PARTNER trial criteria

AS, aortic stenosis; AVA, aortic valve area; BSA, body surface area; CCS, Canadian Cardiovascular Society class; CHF, congestive heart failure; NR, not reported; NYHA, New York Heart Association; PARTNER, Placement of AoRTic TraNscathetER Valve trial; REVIVAL, Transcatheter Endovascular Implantation of Valves trial; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; US, United States, UK, United Kingdom; VA, Veterans Affairs; VHD, valvular heart disease; echo, echocardiography; implantation; V_{max}, peak velocity

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CHAPTER 5

Transcatheter Aortic Valve Replacement in Europe: Adoption Trends and Factors influencing Device Utilization

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ABSTRACT

Objectives

We sought to examine the adoption of transcatheter aortic valve replacement (TAVR) in Western Europe and investigate factors that may influence the heterogeneous use of this therapy.

Background

Since commercialization in 2007, the number of TAVR procedures has grown exponentially.

Methods

The adoption of TAVR was investigated in 11 European countries: Germany, France, Italy, United Kingdom, Spain, Netherlands, Switzerland, Belgium, Portugal, Denmark, and Ireland. Data were collected from two sources: (1) lead physicians submitted nation-specific registry data; (2) an implantation-based TAVR-market tracker. Economic indices such as healthcare expenditure per capita, sources of healthcare funding, and reimbursement strategies were correlated to TAVR utilization. Furthermore, we assessed the extent to which TAVR has penetrated its potential patient population.

Results

Between 2007 and 2011, 34,317 patients underwent TAVR. Considerable variation in TAVR utilization existed across nations. In 2011, the number of TAVR implants per million ranged from 6.1 in Portugal to 88.7 in Germany (mean±standard deviation:33±25). The annual number of TAVR implants performed per center across nations also varied widely (range:10-89). The weighted average TAVR penetration rate was low: 17.9%. Significant correlation was found between TAVR use and healthcare spending per capita ($r = 0.80$, $p = 0.005$). TAVR-specific reimbursement systems were associated with higher TAVR use than restricted systems (698±232 vs. 213±112 implants/million ≥75 years, $p = 0.002$).

Conclusions

Our findings indicate that TAVR is underutilized in high and prohibitive surgical risk patients with severe aortic stenosis. National economic indices and reimbursement strategies are closely linked with TAVR use and help explain the inequitable adoption of this therapy.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) gained Conformité Européenne (CE)-mark approval in 2007, and in subsequent years the number of patients undergoing TAVR in Europe has increased exponentially. Despite the encouraging results from randomized controlled trials and registries,[1-4] there is anecdotal evidence that the utilization of TAVR varies markedly across European nations.

Disparate adoption of medical technology is pervasive and results in inequitable patient access.[5] Adoption kinetics of a novel medical technology such as TAVR and the factors influencing these variables have not been previously described. Regional differences in TAVR adoption are likely to have emerged due to variations in social, regulatory, economic, and political circumstances, as well as disease prevalence and longevity. This information may be of interest to patients, healthcare professionals, regulatory authorities, the medical device industry and healthcare payers. In addition, these data may have implications for healthcare resource allocation, service development planning, assessing equitable patient access, and physician training.

We sought to address this information gap by examining the trends in both the number of TAVR implants and centers across 11 European countries since CE-mark approval. In addition, we investigated factors that may influence the heterogeneous adoption of this novel technology across nations.

METHODS

Data Sourcing

We investigated TAVR utilization in 11 European countries: Germany, France, Italy, the United Kingdom (UK) including Northern Ireland, Spain, the Netherlands, Switzerland, Belgium, Portugal, Denmark and the Republic of Ireland. Data were collected from two distinct sources. Firstly, we identified data from published national registries and large databases in countries where reimbursement is linked to registry inclusion.[3,4,6-8] Lead physicians from each nation submitted data from national registries regarding the annual number of patients treated with TAVR and the annual number of implanting centers from 2007 to 2011. Lead physicians take responsibility for the integrity of the data (Supplementary Table 1).

Secondly, we present data from BIBA MedTech (London, United Kingdom), a cardiovascular market analysis group tracking TAVR utilization since mid-2009. These data were

gathered through specifically designed questionnaires and pre-arranged telephone interviews with an extensive research panel comprising interventional cardiologists, cardiac surgeons and administrators from a large number of TAVR centers throughout Europe. National implant estimates were extrapolated using an algorithm that incorporated the following variables: device pricing; national guidelines; national reimbursement policies; portfolio; spread; and trend. This final dataset was cross-referenced with published registries.

Nation-specific data were combined with European Union derived year-end population estimates to calculate:[9] (1) the annual and cumulative number of TAVR performed in each nation; (2) the annual number of TAVR implants per million of population and TAVR implants per million of population age ≥75 years; (3) the annual and cumulative number of TAVR centers in each nation; (4) the number of TAVR centers per million of population; and (5) the mean number of TAVR implants per center for each nation.

TAVR Penetration

The penetration rate of a therapy is a descriptor of the use of that therapy among eligible patients. Thus, TAVR penetration in each nation was determined as a measure of actual TAVR use relative to potential use. The numerator for calculating penetration was the number of living TAVR recipients at year-end in each country. This was calculated as the sum of patients receiving TAVR in that calendar year and the number of living TAVR recipients from previous years. Annual mortality rates at 1, 2, 3 and 4 years following TAVR were assumed to be 24%, 33%, 49%, 57%, respectively.[10] The denominator was an estimate of the prevalence of patients with symptomatic severe aortic stenosis at high or excessive surgical risk that could potentially be treated with TAVR.[11] Briefly, the proportion of elderly inhabitants of each country ≥75 years of age with severe aortic stenosis (3.4%) was determined by a random-effects meta-analysis. Among these patients, 75.6% were estimated to be symptomatic, 40.5% were deemed to be inoperable due to excessive surgical risk, and among the patients that received surgical aortic valve replacement, 5.2% were determined to be at high operative risk (Society of Thoracic Surgeons risk of mortality ≥10%). Finally, 40.3% of inoperable patients and 80.0% of the high-risk patients were deemed to be potential TAVR candidates.

Economic Indices

National economic indices and healthcare parameters for 2011 were obtained from European Union and Organisation for Economic Co-operation and Development databases.[12] In order to establish economic factors associated with TAVR utilization, we correlated the number of TAVR implants per million (≥75 years) to the volume indexed gross domestic product (GDP) per capita in purchasing power standards (PPS). GDP per capita in PPS

is obtained by converting GDP per capita to a fictive currency using purchasing power parities (PPP) that eliminates differences in currency and price levels between countries, thereby allowing meaningful volume comparisons of GDP. In addition, we correlated the number of TAVR implants per million (≥75 years) with the percentage of GDP spent on healthcare and the PPP-adjusted total healthcare expenditure per capita (United States dollars). In Europe, healthcare is funded either by taxation or by social insurance institutions, which are largely outside the commercial marketplace. We classified healthcare financing in each country according to the principal source of funding and compared TAVR utilization between these systems.

TAVR Reimbursement

Medical device reimbursement in Europe is inconsistent as healthcare regulators with diverse policies dictate the method of reimbursement.[13] We divided existing 2011 TAVR-reimbursement into two categories and compared TAVR use between these schemes: (1) "TAVR-specific" systems where TAVR is completely reimbursed via a therapy-specific national diagnosis related group (DRG) tariff; and (2) "constrained" systems where TAVR reimbursement is only partially funded by an existing national DRG tariff or where the cost is borne by a local healthcare trust or hospital budget.

Statistics

Continuous variables are presented as mean ± standard deviation or median with interquartile range according to distribution. Normally distributed variables were compared with the Student's *t*-test and non-normally distributed variables compared with the Wilcoxon rank-sum test. Categorical variables are presented as numbers and percentages. Bland-Altman plots were used to graphically compare the two sources of TAVR implant data. Correlation between economic indices and TAVR implants per million (≥75 years) was assessed using Pearson's or Spearman's correlation according to distribution. A probability value <0.05 was considered to indicate statistical significance. Analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Data Sourcing

With the exception of one small center (<30 TAVR implants per annum) in both the Netherlands and Belgium, complete data were available from the 11 study nations. Herein, we report the results from the national databases which include TAVR implant data since CE-mark approval in 2007. The BIBA MedTech dataset includes data from 2009 to 2011 and is presented as Appendix.

Implantation Rates

Between January 2007 and December 2011, a total of 34,317 patients underwent TAVR in the 11 study nations (Figure 1A). Almost half of all implants were performed in Germany (45.9%), with Italy (14.9%) and France (12.9%) the next most frequent implanters (Table 1). Ireland accounted for the smallest proportion of implants (0.4%). In 2011, the highest annual increase in procedural volume was observed in France (61%) and Germany (49%), while Ireland (−15%) and Portugal (−3%) were the only nations to experience a decline. The annual number of implants increased 33-fold from 455 in 2007 to 14,946

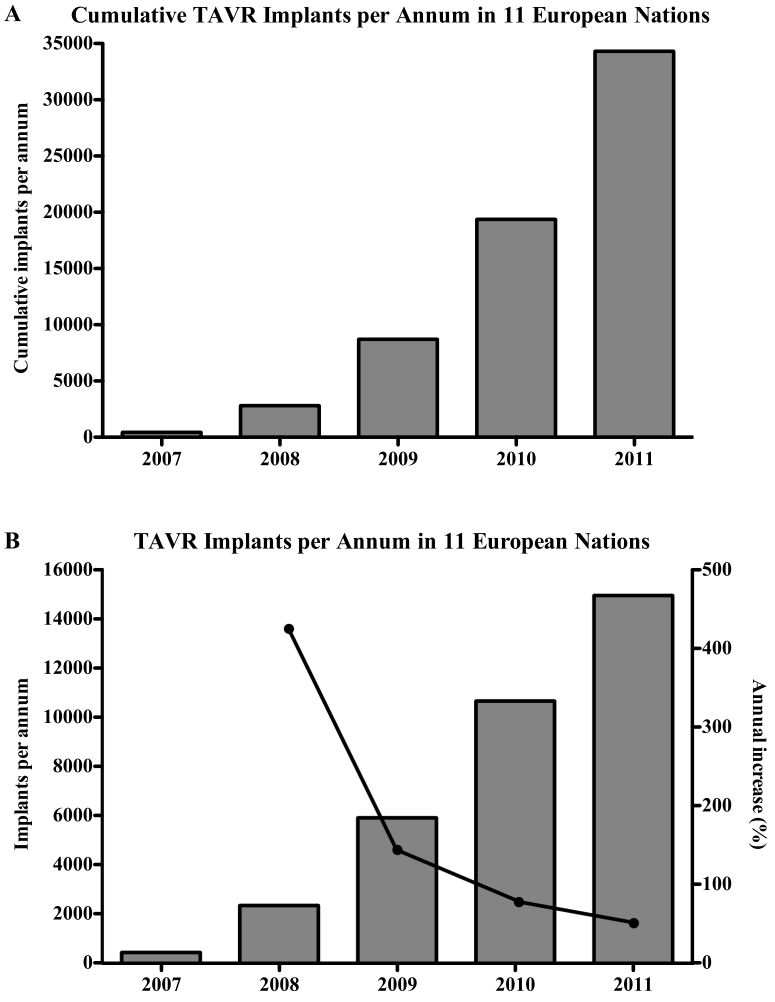

Figure 1. TAVR Adoption in Europe
(A) Cumulative TAVR implants in 11 Western European nations between 2007 and 2011; and (B) TAVR implants per annum and percentage annual increase (solid line).
TAVR = transcatheter aortic valve replacement.

Table 1. TAVR Implants in Each Nation

	TAVR implants per annum (% increase)					Cumulative TAVR	Cumulative TAVR (%)
	2007	2008	2009	2010	2011		
Germany	157	921 (487)	2,566 (179)	4,859 (89)	7,252 (49)	15,755	45.9
France	58	82 (41)	320 (290)	1,523 (376)	2,447 (61)	4,430	12.9
Italy	71	450 (534)	1,138 (153)	1,581 (39)	1,879 (19)	5,119	14.9
United Kingdom	66	295 (347)	561 (90)	778 (39)	1,037 (33)	2,737	8.0
Spain	12	151 (1,158)	426 (182)	655 (54)	770 (18)	2,014	5.9
Netherlands*	40	123 (208)	226 (84)	329 (46)	438 (33)	1,156	3.4
Switzerland	18	127 (606)	277 (118)	382 (38)	501 (31)	1,305	3.8
Belgium*	10	100 (900)	163 (63)	257 (58)	289 (12)	819	2.4
Portugal	4	13 (225)	52 (300)	67 (29)	65 (−3)	201	0.6
Denmark	9	81 (800)	126 (56)	190 (51)	239 (26)	645	1.9
Ireland	0	12	61 (408)	34 (−44)	29 (−15)	136	0.4
Total (% increase)	445	2,355 (429)	5,916 (151)	10,655 (81)	14,946 (40)	34,317	100

Data are actual numbers and percentages. * Excludes one low-implant volume center (<30 TAVR implants per annum) in both the Netherlands and in Belgium. TAVR, transcatheter aortic valve replacement.

in 2011 (Figure 1B). Although the annual procedural volume growth rate has decreased from 429% in 2008 to 40% in 2011, it remained positive.

We observed a wide variation in the number of TAVR implants per million of population (Figure 2 A, B). Germany (88.7) and Portugal (6.1) accounted for the highest and lowest number of TAVR implants per million of population in 2011, respectively. Among the 11 study nations, the mean number of TAVR implants per million was 32.9±24.9 while the mean number of TAVR implants per million ≥75 years was 398±283.

Implanting Centers

The number of centers performing TAVR increased approximately 9-fold from 37 in 2007 to 342 in 2011 (Figure 3A). In 2011, Germany (90) and Italy (87) had the highest number of TAVR centers whereas Portugal, Denmark and Ireland (3) had the lowest (Table 2). Belgium had the highest number of TAVR centers per million of population (2.1) and Portugal (0.3) the lowest (Figure 3B). On average, there were 0.9±0.6 TAVR centers per million of population. These numbers led to an average of 41±28 TAVR implants per center in 2011, with estimates in individual countries ranging from 10 in Ireland to 89 in Germany (Figure 3C). On account of the high number of TAVR centers per million of population, Belgium had the second lowest number of TAVR implants per center (13).

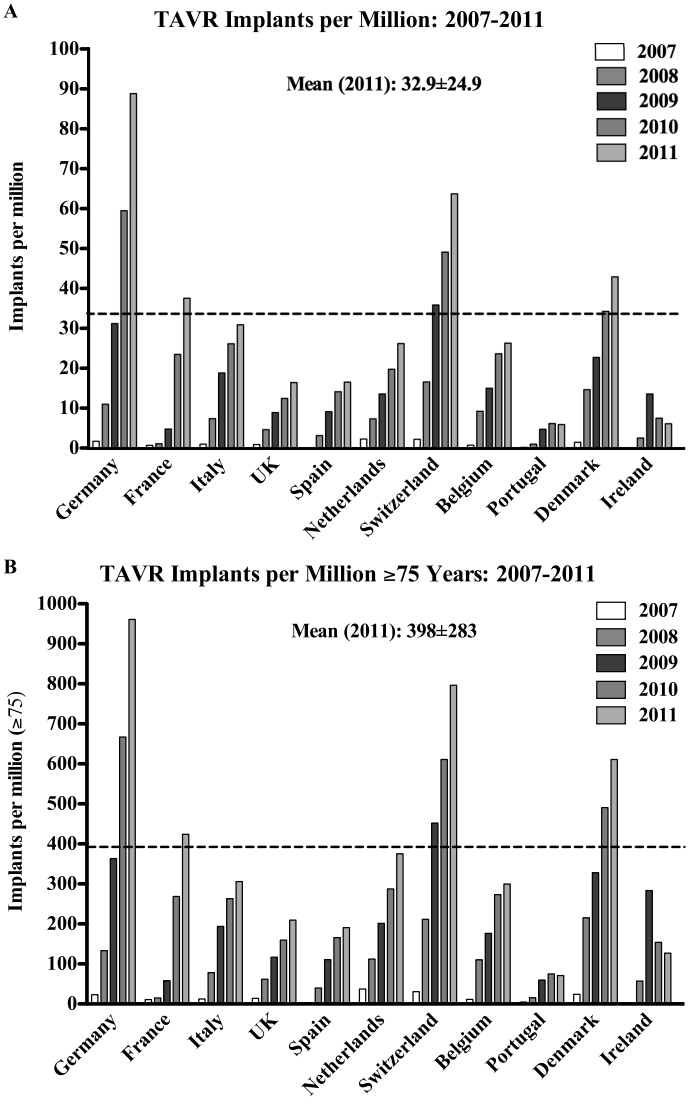

Figure 2. TAVR Implants per Million in the Study Nations

TAVR implant dynamics in the study nations between 2007 and 2011: (A) TAVR implants per million of population; and (B) TAVR implants per million ≥75 years old. Broken line represents mean. Abbreviation as in Figure 1.

TAVR Penetration

In 2011, we estimate that there were 28,400 living TAVR recipients and 158,371 potential TAVR candidates in the 11 study nations (Table 3). Thus, the calculated weighted average TAVR penetration rate in 2011 was 17.9%. The estimated collective and nation-specific TAVR penetration rates are presented in Figure 4 (A, B). Germany (36.2%) and

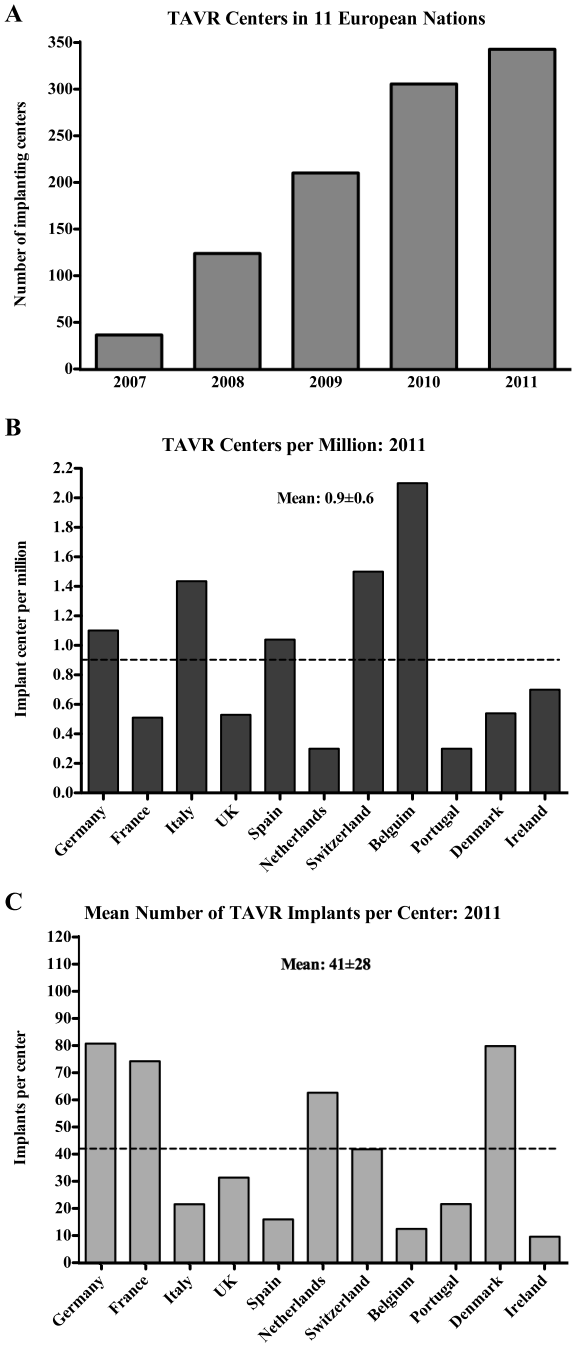

Figure 3. TAVR Centers in Europe

(A) Cumulative TAVR centers in 11 Western European nations from 2007 to 2011; (B) TAVR centers per million of population in 2011; and (C) mean number of TAVR implants per center in each nation in 2011. Broken line represents mean. Abbreviation as in Figure 1.

Table 2. Implant Centers

	Cumulative TAVR centers					TAVR centers, 2011 (%)	TAVR centers per million, 2011	TAVR implants per center, 2011
	2007	2008	2009	2010	2011			
Germany	6	36	61	80	90	26.3	1.1	81
France	6	12	16	33	33	9.6	0.5	74
Italy	8	21	50	75	87	25.4	1.4	22
United Kingdom	6	19	26	31	33	9.6	0.5	31
Spain	2	10	20	39	48	14.0	1.0	16
Netherlands	3	6	7	7	7	2.0	0.4	63
Switzerland	1	7	8	11	12	3.5	1.5	42
Belgium	2	7	13	20	23	6.7	2.1	13
Portugal	1	2	3	3	3	0.9	0.3	22
Denmark	2	3	3	3	3	0.9	0.5	80
Ireland	0	1	3	3	3	0.9	0.7	10
Total	37	124	210	305	342	100	0.9±0.6	41±28

Data are actual number or mean ± SD. Abbreviation as in Table 1.

Switzerland (34.5%) had the highest TAVR penetration rates; Portugal (3.4%) and Spain (8.4%) had the lowest penetration rates.

Economic Indices

We assessed the association between several economic indices and TAVR use (Table 4). The volume indexed GDP per capita, which is considered to be a reliable indicator of a country's standard of living, was not associated with TAVR use ($r = 0.53$, $p = 0.10$: Figure 5A). In contrast, a significant linear correlation was found between the number of TAVR implants per million (≥75 years) and healthcare spending as a percentage of GDP ($r = 0.68$, $p = 0.025$: Figure 5B), and healthcare spending per capita ($r = 0.80$, $p = 0.005$: Figure 5C). We also found an association between the principal source of healthcare funding and the number of TAVR implants per million (Figure 5D). Although not statistically significant, there was a trend towards increased TAVR use in those nations where healthcare was funded principally by social insurance (Germany, France, the Netherlands, Switzerland, and Belgium) than those principally funded by taxation (Italy, UK, Spain, Portugal, Denmark, Ireland) (571±290 versus 252±192 implants per million ≥75 years, $p = 0.056$).

TAVR Reimbursement

TAVR reimbursement strategies across the study nations were heterogeneous (Table 4, Figure 6). TAVR-specific national DRG-based reimbursement occurs in Germany, France, Switzerland, and Denmark. Constrained reimbursement systems were noted for the UK,

Table 3. TAVR Penetration: 2011

	Total Population, 2011	Population ≥ 75 years old, 2011	Severe AS (3.4%)	Symptomatic severe AS (75.6%)	Ineligible for SAVR		Eligible for SAVR			Total TAVR eligible	TAVR penetration, 2011 (%)
					Ineligible for SAVR (40.5%)	TAVR eligible (40.3%)	Eligible for SAVR (59.5%)	High-risk (5.2%)	TAVR eligible (80%)		
Germany	81,751,602	7,546,760	256,590	193,982	78,563	31,661	115,419	6,002	4,801	36,462	36.2
France	65,048,412	5,771,830	196,242	148,359	60,085	24,214	88,274	4,590	3,672	27,887	13.9
Italy	60,626,442	6,147,116	209,002	158,005	63,992	25,789	94,013	4,889	3,911	29,700	13.8
United Kingdom	62,498,612	4,947,416	168,212	127,168	51,503	20,756	75,665	3,935	3,148	23,903	9.1
Spain	46,152,926	4,031,995	137,088	103,638	41,947	16,915	61,665	3,207	2,565	19,481	8.4
Netherlands	16,655,799	1,166,868	39,647	29,993	12,147	4,895	17,846	928	742	5,638	16.3
Switzerland	7,870,134	629,004	21,386	16,168	6,548	2,639	9,620	500	400	3,039	34.5
Belgium	10,951,266	954,607	32,457	24,537	9,938	4,005	14,600	759	607	4,612	14.1
Portugal	10,529,255	964,125	32,780	24,782	10.037	4,045	14,745	767	613	4,658	3.4
Denmark	5,560,628	391,138	13,299	10,054	4,072	1,641	5,982	311	249	1,890	27.1
Ireland	4,569,864	227,917	7,749	5,858	2,373	956	3,486	181	145	1,101	9.2
Total	376,049,328	32,778,776	1,114,478	842,546	341,230	137,516	501,315	26,068	20,855	145,962	Weighted average: 17.9

Population data derived from EU sources.[9] Estimates of TAVR-eligible patients derived from Osnabrugge RL et al.[11] AS, aortic stenosis; SAVR, surgical aortic valve replacement; other abbreviation as in Table 1.

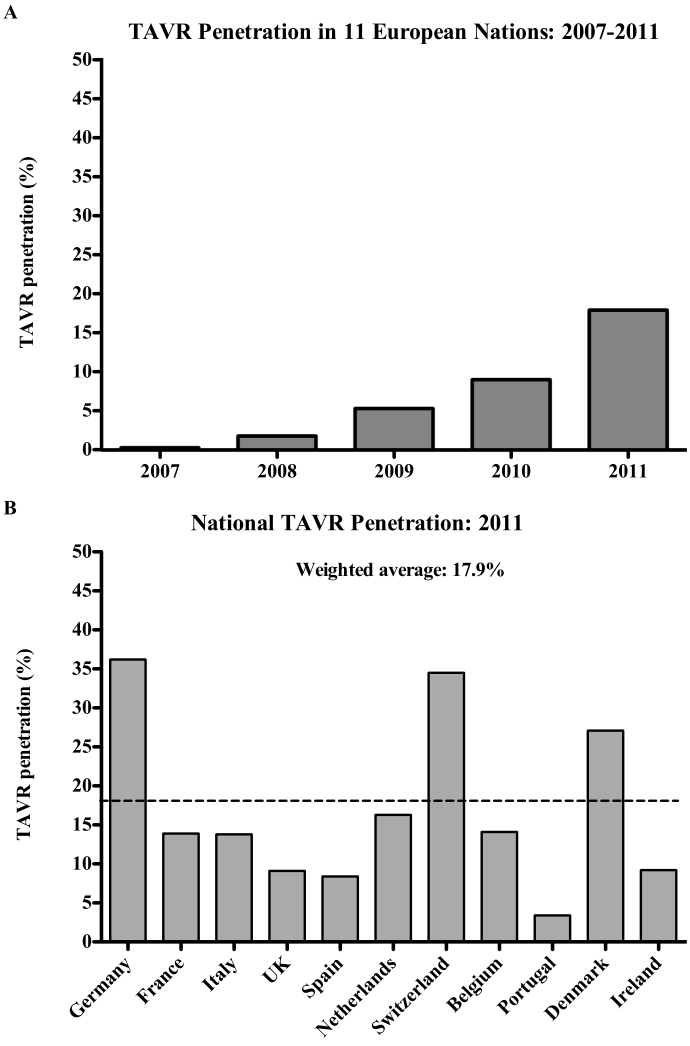

Figure 4. TAVR Penetration in Europe
(A) Estimated TAVR penetration among the 11 study nations from 2007 to 2011; and (B) TAVR penetration in each nation in 2011. Broken line represents weighted average. Abbreviation as in Figure 1.

Spain, the Netherlands, Belgium, Portugal and Ireland where the cost of TAVR is borne by a local healthcare trust (UK) or by the hospital budget. Reimbursement systems evolved over the course of the study. For example, a TAVR-specific DRG was introduced in Germany in January 2008 as opposed to France where it was introduced in December 2009.

We investigated the association between reimbursement system and both TAVR utilization (implants per million ≥75 years) and the number of TAVR implants per center. Italy was excluded from the analysis as reimbursement strategies varied across provinces.

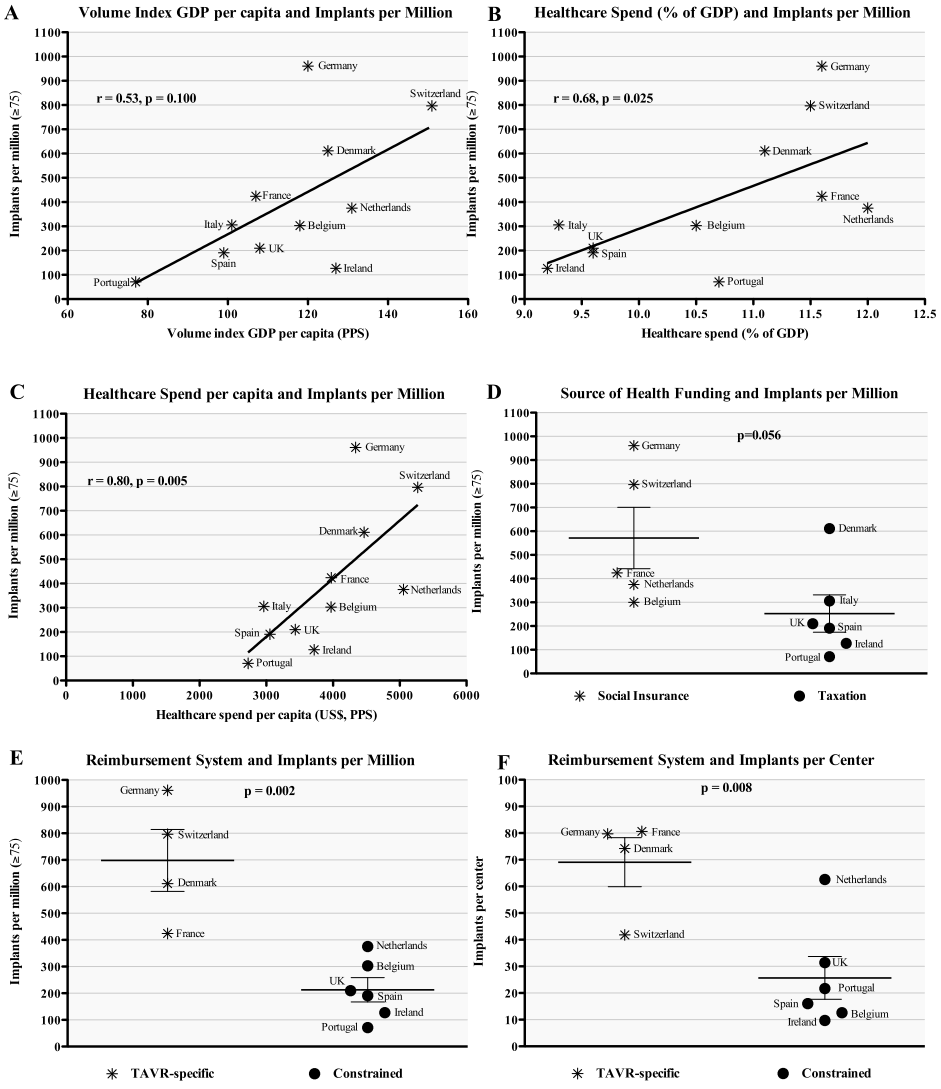

Figure 5. Factors Influencing TAVR Adoption in Europe

(A) Correlation between TAVR implants per million (≥75 years) and (A) volume indexed gross domestic product (GDP), (B) healthcare expenditure (% of GDP), and (C) annual healthcare spend per capita (US dollars). Number of TAVR implants per million (≥75 years) according to (D) the principle source of healthcare funding (social insurance or taxation), and (E) the system of reimbursement (TAVR-specific or constrained). (F) The average number of TAVR implants per center in 2011 and the system of reimbursement. DRG, diagnosis related group; PPS, purchasing power standards; other abbreviation as in Figure 1.

TAVR-specific reimbursement systems were associated with a 3.3-fold higher number of TAVR implants per million (≥75 years) than constrained systems (698±232 versus 213±112, $p = 0.002$: Figure 5E). Furthermore, TAVR-specific reimbursement systems

Table 4. Economic Indices and Reimbursement Schemes

	Volume indexed GDP per capita (PPP)	Healthcare spend (% of GDP)	Healthcare spend per capita (2010, US$, PPP)	Principle source of healthcare funding	TAVR reimbursement
Germany	120	11.6	4,338	Social insurance	National TAVR DRG
France	107	11.6	3,974	Taxation	National TAVR DRG
Italy	101	9.3	2,964	Taxation	Region dependent
United Kingdom	108	9.6	3,433	Taxation	Cost borne by local trust
Spain	99	9.6	3,056	Taxation	Cost borne by hospital
Netherlands	131	12.0	5,056	Social insurance	Cost borne by hospital
Switzerland	151	11.5	5,270	Social insurance	National TAVR DRG
Belgium	118	10.5	3,969	Social insurance	Cost borne by hospital
Portugal	77	10.7	2,728	Taxation	National SAVR DRG. Remainder of cost borne by hospital
Denmark	125	11.1	4,464	Taxation	National TAVR DRG
Ireland	127	9.2	3,718	Taxation	Cost borne by hospital

Values are actual numbers. GDP, gross domestic product; US$, United States dollars; PPP, purchasing power parity; DRG, diagnosis related group; SAVR, surgical aortic valve replacement.

were associated with 2.5 times more TAVR implants per center than constrained systems (69±18 vs. 26±20 implants per center ($p = 0.008$, Figure 5F).

Comparison Between Registry and BIBA Datasets

The correlation between national registry and BIBA MedTech datasets for TAVR implant numbers is presented by a Bland-Altman plot (Supplementary Figure 1). There was satisfactory agreement between the two sources of information and both provided similar results and conclusions (Supplementary Tables 2-5, Figures 2-6).

DISCUSSION

This study describes the adoption of TAVR in 11 Western European nations since the 2007 CE mark approval of the Edwards Sapien (Edwards Lifesciences Inc., Irvine, CA, USA) and Medtronic CoreValve (Medtronic Inc., Minneapolis, MN, USA) systems. The main findings are: (1) more than 34,000 patients received TAVR between 2007 and 2011; (2) there is substantial variation in the adoption of TAVR across nations; (3) there is disparity

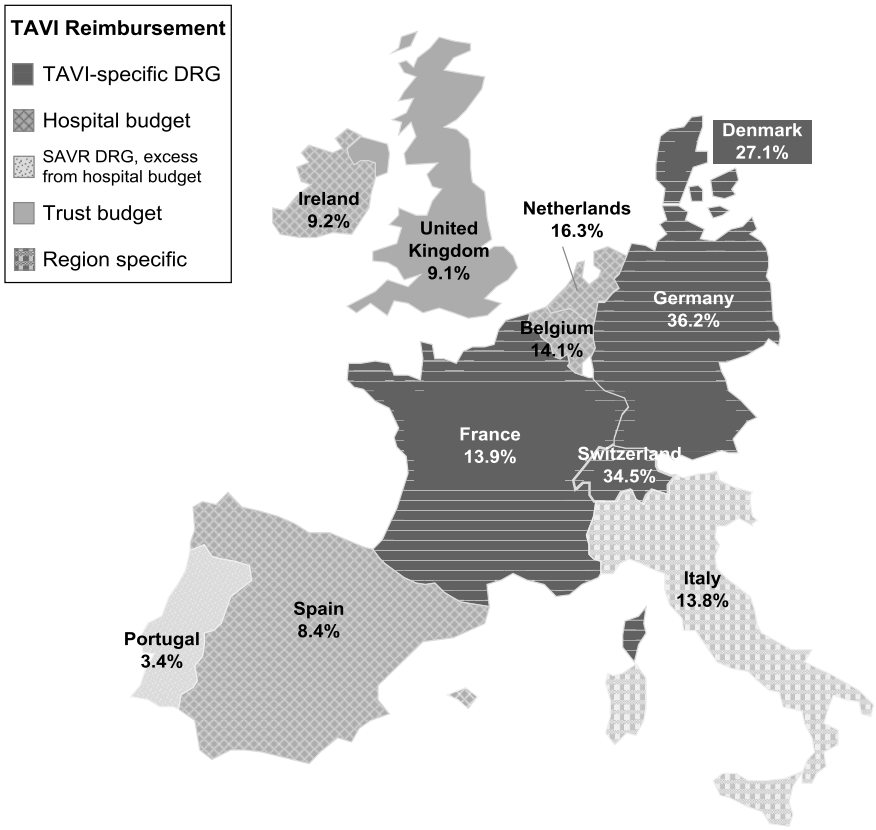

Figure 6. Reimbursement Systems and TAVR Penetration across Europe
Map of the 11 study nations depicting estimated TAVR penetration rate and the 2011 TAVR-reimbursement systems. DRG, diagnosis-related group; SAVR, surgical aortic valve replacement; other abbreviation as in Figure 1.

in the annual number of TAVR implants per center across nations (mean: 41±28); (4) TAVR remains greatly underutilized with an estimated weighted penetration rate of 17.9%; and (5) economic and reimbursement indices may help explain the variability in TAVR adoption across nations.

We found considerable variation in TAVR utilization across nations. Germany had more than two times the implant rate of all other nations except Switzerland, and 14 times the implant rate of Ireland and Portugal. Regional variation in the adoption of medical technology is not unique to TAVR. In Europe, disparate use of drug-eluting stents (DES) and implantable cardioverter defibrillators (ICD) has previously been described.[5,14,15] The identification of inequitable access to medical technologies is important as it generates discussion and initiatives to address inequalities and the corresponding impact on patient outcomes through payer and physician led programs (E.g. Stent for Life Initiative).[16]

Explanations for the divergence in TAVR adoption among countries are numerous and varied. The economic challenge of providing progressive care for an ageing population has mandated that the utilization of new medical device technologies be not only determined by the expectation of improved clinical outcomes, but also by cost-effectiveness. It is axiomatic therefore, that the magnitude of healthcare resources influences the adoption of new medical device technology. Consistent with our findings that healthcare expenditure correlated with TAVR utilization, the use of ICDs in Europe has also been associated with national economic performance.[5,14] Not surprisingly, the lowest TAVR implantation rates were found in Spain, Portugal and Ireland who are currently experiencing substantial economic hardship. In these nations, the medical device industry could provide additional support to develop and maintain TAVR programs. As was the case with DES and ICDs, the introduction of competitive TAVR systems should decrease procedural costs and consequently increase TAVR adoption.

Procedural reimbursement and healthcare funding are critical factors in determining the adoption of new medical device technology. Previously, these factors have been shown to influence the use of ICDs and coronary stents. In the current study, TAVR utilization and the number of TAVR implants per center were found to be higher in the presence of nationwide TAVR-specific reimbursement schemes than restrictive reimbursement schemes. The impact of restrictive reimbursement systems was evident in the UK, Spain, the Netherlands, Belgium, Portugal, and Ireland. We also observed a trend towards increased TAVR use in nations where social insurance rather than taxation was the principle source of healthcare funding ($p = 0.056$).

Our estimates of TAVR penetration suggest that TAVR remains underutilized in Western Europe. While the TAVR penetration rate in 2011 was >30% in Germany and Switzerland, the weighted average penetration among the 11 nations studied was 17.9%, and penetration rates were <15% in two thirds of the countries. The adoption of new technology can be a slow process. It requires a threshold of robust clinical evidence, device iteration, physician training, clinical and financial planning. Moreover, the cultural change required to embrace new therapies often evolves gradually. Given the therapeutic benefit associated with TAVR in inoperable patients (number needed to treat = 5) (1), the demonstrable cost-effectiveness in both excessive and high-risk cohorts,[17-19] and the less invasive nature of TAVR procedures, the protracted uptake of TAVR technology may have negative consequences for patients, physicians, and administrators. Although TAVR penetration is not necessarily a surrogate for quality of medical care, it may suggest the need for enhanced patient access to novel and potentially life-saving therapies. Indeed, it is interesting to speculate that in nations with higher TAVR penetration rates, a move towards treating patients at less extreme surgical risk may be emerging.[20]

The impressive clinical trial outcomes with TAVR are attributable, in part, to the participation of experienced physicians and institutions. These outcomes are not necessarily reproducible in lower-volume settings.[21-23] For these reasons, volume-based guidelines for catheter-based and surgical procedures exist.[24,25] The recommended centralization of TAVR procedures in high-volume tertiary referral centers aims to ensure adequate operator and center volume for these complex procedures.[26-28] National health technology assessments and position papers have suggested that each center perform a minimum of 24 TAVR procedures per annum.[27,29,30] We observed centers with low procedural volume and therefore non-adherence to these criteria in several nations. In particular, centers in Ireland, Belgium and Spain performed on average less than 20 implants in 2011. Two distinct observations explain the low procedural volume: (1) low number of TAVR implants per million (Ireland); and (2) an excessive number of TAVR centers (Belgium and Spain). The reasons for the variation in the number of TAVR centers per million and center volume across nations are unclear. National political and financial concerns, healthcare policy, population density and profile, reimbursement strategy, and cultural factors may be important in determining the number of centers in each nation.

The way complex medical technology is disseminated has been revolutionized by TAVR. Clinical site selection, mandatory physician and team training, and detailed algorithms outlining patient selection have become the standard of care. Nevertheless, the variation in the adoption of TAVR in Western Europe is clear. Physicians, medical societies, the medical device industry, and other stakeholders have a responsibility to ensure the appropriate use and sensible dispersion of this innovative technology.

Limitations

Several limitations are of note. Firstly, although every attempt was made to ensure the validity of the implant data, both data sources should be considered to be estimates. Registry data may underestimate the true scale of TAVR use as some cases or small implant centers may not have been included. Secondly, the estimates of TAVR use are likely to have included patients treated for off-label indications, such as patients at lower surgical risk, which may have affected the estimates of TAVR penetration.

Conclusions

Despite the rapid adoption of TAVR across Europe, our findings indicate that a sizeable treatment gap remains for high/prohibitive surgical risk patients with severe aortic stenosis. National economic indices and reimbursement strategies are closely linked with TAVR use and may explain the inequitable adoption of TAVR across nations.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contributions of Dario Remigi of BIBA MedTech and Rachele Busca of Medtronic in developing this project.

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APPENDIX

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Supplementary Table 1. Sources of National Registry Data

Country	Physician	Institution
Germany	Ruediger Lange	German Heart Center, Munich
France	Thierry Lefèvre	Institut Cardiovasculaire Paris Sud, Massy
Italy	Francesco Maisano	San Raffaele Hospital, Milan
United Kingdom	Neil Moat	Royal Brompton Hospital and on behalf of NICOR, London
Northern Ireland	Ganesh Manoharan	The Heart Centre, Royal Victoria Hospital, Belfast
Spain	Eulogio Garcia	Hospital Clínico San Carlos, Madrid
Netherlands	Peter de Jaegere	Erasmus University Medical Center, Rotterdam
Switzerland	Peter Wenaweser	Bern University Hospital, Bern
Belgium	Johan Bosmans	University of Antwerp, Wilrijk
Portugal	Rui C Teles	Hospital de Santa Cruz, Lisbon
Denmark	Lars Søndergaard	Rigshospitalet, Copenhagen
Ireland	Darren Mylotte	University Hospital, Galway

Supplementary Table 2. TAVR Implants in Each Nation (BIBA Medical)

	TAVR implants per annum (% increase)			Cumulative TAVR	Cumulative TAVR (%)
	2009	2010	2011		
Germany	1,693	6,282 (271)	7,916 (26)	15,891	45.4
France	416	1,579 (280)	2,328 (47)	4,323	12.3
Italy	573	1,602 (180)	2,175 (36)	4,350	12.4
United Kingdom	376	1,068 (184)	1,244 (16)	2,688	7.7
Spain	344	952 (177)	1,082 (14)	2,378	6.8
Netherlands	294	809 (175)	793 (−2)	1,896	5.4
Switzerland	228	602 (164)	618 (3)	1,448	4.1
Belgium	147	437 (197)	552 (26)	1,136	3.2
Portugal	40	84 (110)	74 (−12)	198	0.6
Denmark	125	214 (71)	339 (58)	678	1.9
Ireland	N/A	19	22	41	0.1
Total (% increase)	4236	13,648 (222.2)	17,143 (25.6)	35,027	100

Data represents as actual number and percentage growth.

Supplementary Table 3. TAVR Centers (BIBA Medical)

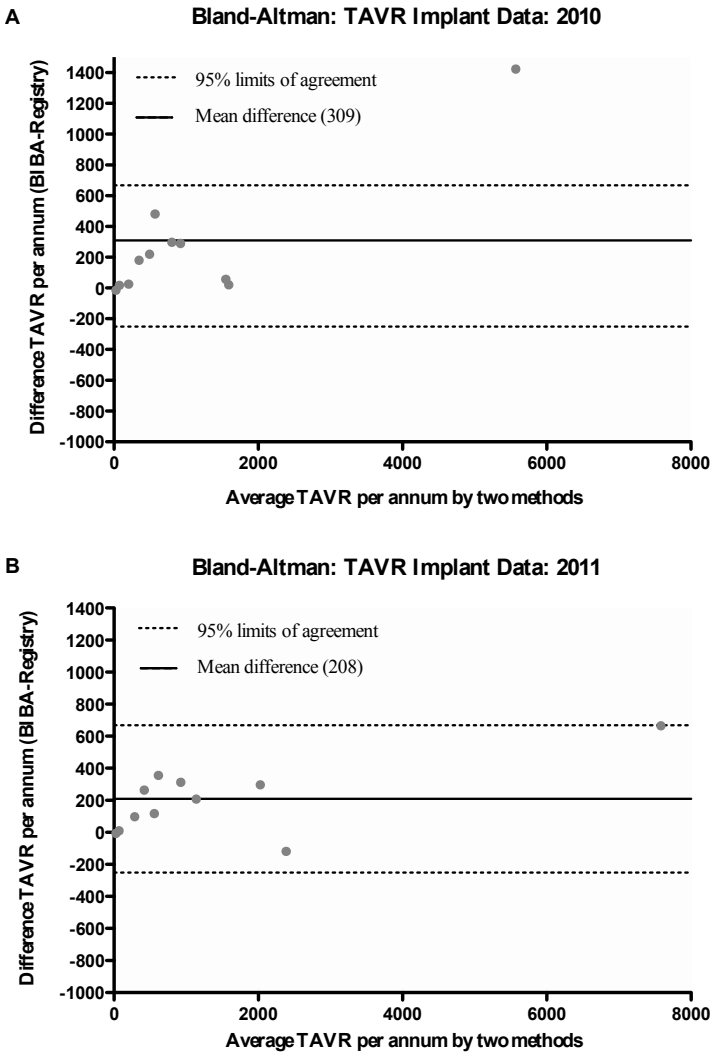
	TAVR centers		TAVR centers (%)	TAVR centers per million, 2011	TAVR implants per center, 2011
	2010	2011			
Germany	59	69	25.5	0.8	115
France	34	34	12.5	0.5	68
Italy	44	53	19.6	0.9	41
United Kingdom	24	32	11.8	0.5	39
Spain	27	29	10.7	0.6	37
Netherlands	14	14	5.2	0.8	57
Switzerland	10	10	3.7	1.3	62
Belgium	6	20	7.4	1.8	28
Portugal	2	3	1.1	0.3	25
Denmark	3	4	1.5	0.7	85
Ireland	3	3	1.1	0.7	7
Total	226	271	100	Mean±SD 0.8±0.4	Mean±SD 51±30

Data represents actual number or mean ± SD.

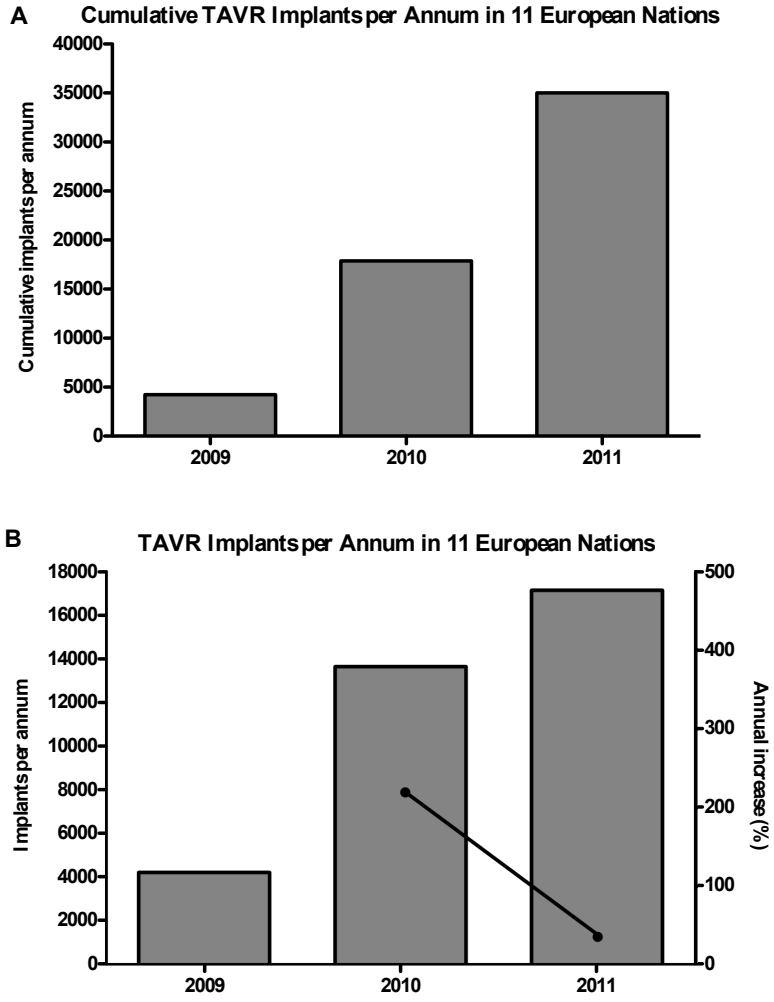
Supplementary Table 4. TAVR Penetration: 2011 (BIBA Medical)

	Total Population, 2011	Population ≥ 75 years old, 2011	Severe AS (3.4%)	Symptomatic severe AS (75.6%)	Ineligible for SAVR		Eligible for SAVR			Total TAVR eligible	TAVR penetration, 2011 (%)
					Ineligible for SAVR (40.5%)	TAVR eligible (40.3%)	Eligible for SAVR (59.5%)	High-risk (5.2%)	TAVR eligible (80%)		
Germany	81,751,602	7,546,760	256,590	193,982	78,563	31,661	115,419	6,002	4,801	36,462	29.0
France	65,048,412	5,771,830	196,242	148,359	60,085	24,214	88,274	4,590	3,672	27,887	10.7
Italy	60,626,442	6,147,116	209,002	158,005	63,992	25,789	94,013	4,889	3,911	29,700	9.9
United Kingdom	62,498,612	4,947,416	168,212	127,168	51,503	20,756	75,665	3,935	3,148	23,903	7.3
Spain	46,152,926	4,031,995	137,088	103,638	41,947	16,915	61,665	3,207	2,565	19,481	7.9
Netherlands	16,655,799	1,166,868	39,647	29,993	12,147	4,895	17,846	928	742	5,638	21.0
Switzerland	7,870,134	629,004	21,386	16,168	6,548	2,639	9,620	500	400	3,039	30.1
Belgium	10,951,266	954,607	32,457	24,537	9,938	4,005	14,600	759	607	4,612	16.4
Portugal	10,529,255	964,125	32,780	24,782	10.037	4,045	14,745	767	613	4,658	2.6
Denmark	5,560,628	391,138	13,299	10,054	4,072	1,641	5,982	311	249	1,890	25.1
Ireland	4,569,864	227,917	7,749	5,858	2,373	956	3,486	181	145	1,101	2.4
Total	376,049,328	32,778,776	1,114,478	842,546	341,230	137,516	501,315	26,068	20,855	145,962	Weighted average: 14.7

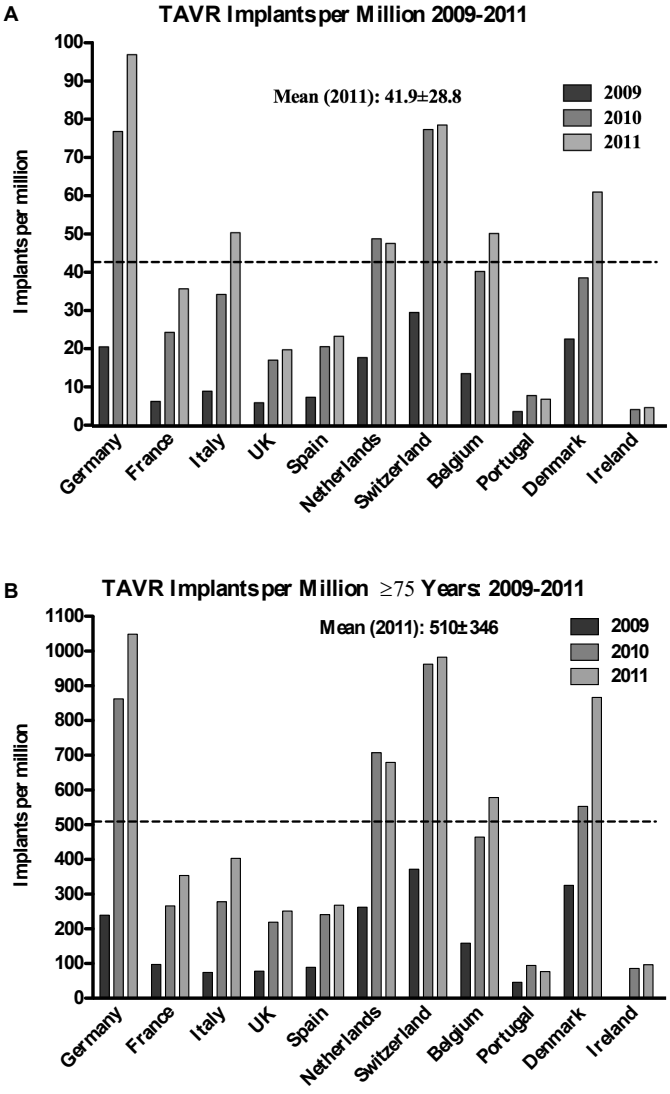
Population data derived from EU sources.[9] Estimates of TAVR-eligible patients derived from Osnabrugge RL et al.[11] AS aortic stenosis; SAVR surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement



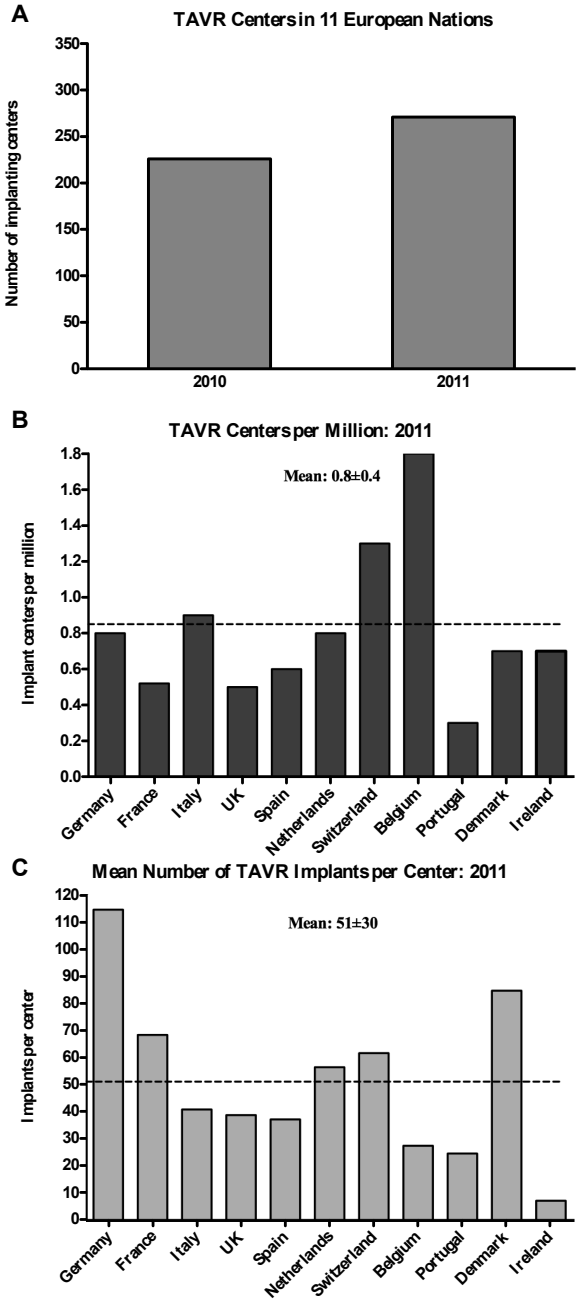
Supplementary Figure 1. Comparison of Registry and BIBA MedTech Datasets
Bland-Altman plots comparing national TAVR implants per annum between the registry and BIBA medical data sources. In each plot, the solid line represents the mean difference, and the dashed line represents two standard deviations. TAVR = transcatheter aortic valve replacement.



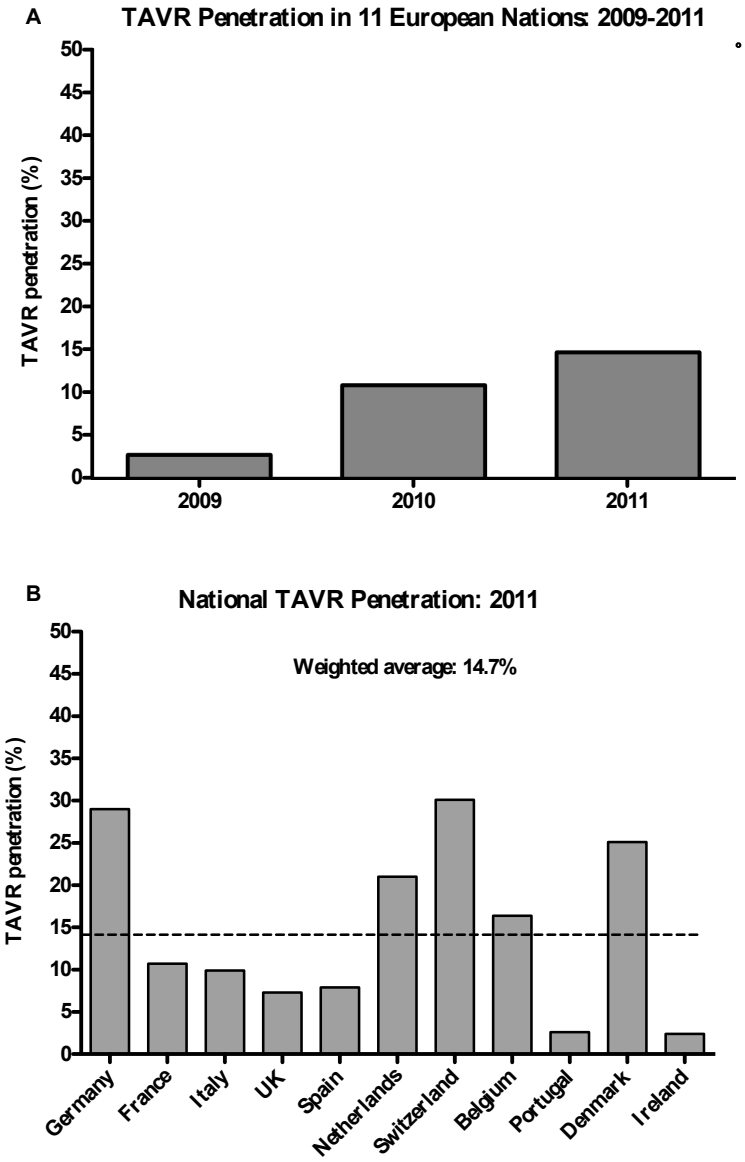
Supplementary Figure 2. TAVR Adoption in Europe (BIBA Medical)
(A) Cumulative TAVR implants in 11 Western European nations between 2009 and 2011; and (B) TAVR implants per annum and percentage annual increase (solid line). TAVR = transcatheter aortic valve replacement.



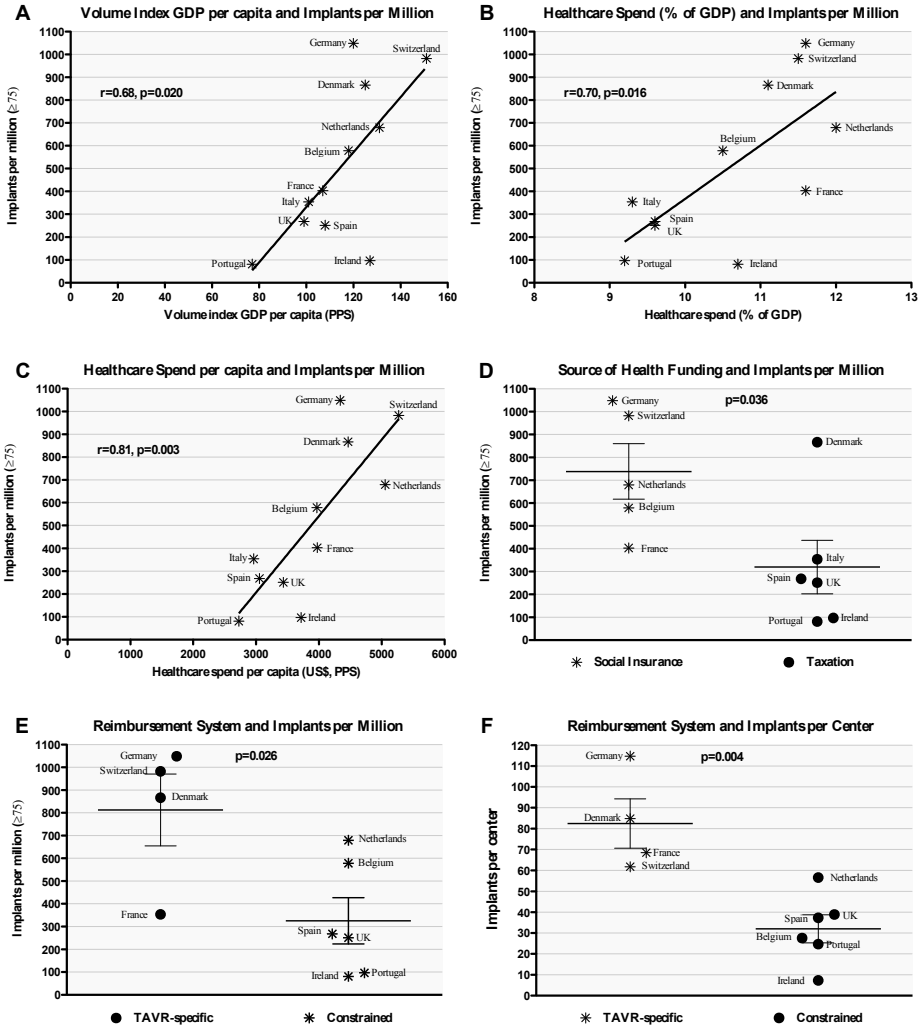
Supplementary Figure 3. TAVR Implants per Million Population in the Study Nations (BIBA Medical)
TAVR implant dynamics in the study nations between 2009 and 2011: (A) TAVR implants per million of population; and (B) TAVR implants per million ≥75 years old. Broken line represents mean. Abbreviation as in Supplementary Figure 2.



Supplementary Figure 4. TAVR Centers in Europe (BIBA Medical)
(A) Cumulative TAVR centers in 11 Western European nations in 2010 and 2011; (B) TAVR centers per million of population in 2011; and (C) mean number of TAVR implants per center in each nation in 2011. Broken line represents mean. Abbreviation as in Supplementary Figure 2.



Supplementary Figure 5. TAVR Penetration in Europe (BIBA Medical)
(A) Estimated TAVR penetration among the 11 study nations from 2009 to 2011; and (B) TAVR penetration in each nation in 2011. Broken line represents weighted average. Abbreviation as in Supplementary Figure 2.



Supplementary Figure 6. Factors Influencing TAVR Adoption in Europe (BIBA Medical)

Legend. (A) Correlation between TAVR implants per million (≥75 years) and (A) volume indexed gross domestic product (GDP), (B) healthcare expenditure (% of GDP), and (C) annual healthcare spend per capita (US dollars). Number of TAVR implants per million (≥75 years) according to (D) the principle source of healthcare funding (social insurance or taxation), and (E) the system of reimbursement (TAVR-specific or constrained). (F) The average number of TAVR implants per center in 2011 and the system of reimbursement. PPS = purchasing power standards. DRG = diagnosis-related group. Other abbreviation as in Supplementary Figure 2.

CHAPTER 6

Health Status after Transcatheter Aortic Valve Replacement in Patients at Extreme Surgical Risk: Results from the CoreValve U.S. Trial

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JACC Cardiovasc Interv. 2014; In Press.

ABSTRACT

Background and Objectives

For many patients considering TAVR, improvement in quality of life may be of even greater importance than prolonged survival.

The aim of this study was to characterize health status outcomes after transcatheter aortic valve replacement (TAVR) with a self-expanding bioprosthesis among patients at extreme surgical risk and to identify pre-procedural patient characteristics associated with a poor outcome.

Methods

Patients with severe, symptomatic aortic stenosis who were considered to be at prohibitive risk for surgical aortic valve replacement were enrolled in the single-arm CoreValve U.S. Extreme Risk Study. Health status was assessed at baseline and at 1, 6, and 12 months after TAVR using the Kansas City Cardiomyopathy Questionnaire (KCCQ), the Short-Form-12 (SF-12), and the EuroQOL-5D. The overall summary scale of the KCCQ (range 0-100; higher scores = better health) was the primary health status outcome. A poor outcome after TAVR was defined as either death, a KCCQ-overall summary score (KCCQ-OS) <45 or a decline in KCCQ-OS of 10 points at 6-month follow-up.

Results

A total of 471 patients underwent TAVR via the transfemoral approach, of whom 436 (93%) completed the baseline health status survey. All health status measures demonstrated considerable impairment at baseline. After TAVR, there was substantial improvement in both disease-specific and generic health status measures, with an increase in the KCCQ-OS of 23.9 points (95% confidence interval [CI] 20.3-27.5) at 1 month, 27.4 points (95% CI 24.2-30.6) at 6 months, 27.4 points (95% CI 24.1-30.8) at 12 months, along with substantial increases in SF-12 scores and EQ-5D utilities as well (all $p < 0.003$ compared with baseline). Nonetheless, 39% of patients had a poor outcome after TAVR. Baseline factors independently associated with poor outcome included wheelchair dependency, lower mean aortic valve gradient, prior CABG, oxygen dependency, very high predicted mortality with surgical AVR, and low serum albumin.

Conclusions

Among patients with severe aortic stenosis, TAVR with a self-expanding bioprosthesis resulted in substantial improvements in both disease-specific and generic health-related quality of life, but there remained a large minority of patients who died or had very poor quality of life despite TAVR. Predictive models based on a combination of clinical factors as well as disability and frailty may provide insight into the optimal patient population for which TAVR is beneficial.

INTRODUCTION

Aortic stenosis is the most common form of valvular heart disease in the elderly and is associated with high morbidity and mortality once cardiac symptoms develop[1]. In patients who are at extreme risk for serious complications during or after surgery, transcatheter aortic valve replacement (TAVR) has been shown to result in substantial reductions in mortality and improvement in quality of life compared with standard therapy[2, 3]. Despite these health benefits, extreme risk patients who undergo TAVR have high rates of both short- and long-term mortality, with mortality rates of 30% and 43% at 1 and 2 years, respectively[2, 4]. Moreover, given the advanced age and multiple comorbid conditions that are invariably present in the extreme risk population, improvements in quality of life may be of even greater importance than improved survival.

The CoreValve transcatheter heart valve (Medtronic, Inc., Minneapolis, MN) is a self-expanding bioprosthesis that is widely used outside the U.S. In a recently completed trial, the CoreValve was shown to be safe and effective for patients with symptomatic severe aortic stenosis at extreme risk for surgical valve replacement[5], but the quality of life benefits of this device are unknown. To address this gap in knowledge, we sought to characterize health status outcomes among patients at extreme surgical risk who were enrolled in the CoreValve U.S. Pivotal Trial. Our secondary objective was to identify pre-procedural patient characteristics (including comorbidities, surgical risk scores, and measures of frailty and disability) associated with a poor outcome after self-expanding TAVR.

METHODS

Study Design and Patient Population

The design and results of the CoreValve U.S. Extreme Risk Pivotal Trial have been reported previously[5]. Briefly, the trial enrolled patients with severe aortic stenosis and New York Heart Association class II, III or IV heart failure symptoms. Patients were classified as extreme risk if the 30-day risk of mortality or irreversible morbidity was estimated to be ≥50% by 2 cardiac surgeons and 1 interventional cardiologist[5]. In the screening process, each patient was reviewed in detail by a national screening committee that included at least 2 cardiac surgeons and 1 interventional cardiologist, each of whom had to agree that the patient met eligibility, risk, and imaging criteria for the trial. After confirmation by the trial oversight committee, patients underwent TAVR via an iliofemoral approach, using the Medtronic self-expanding CoreValve system (Medtronic, Inc., Minneapolis, MN).

The study was approved by the institutional review board at each site, and all patients provided written informed consent prior to participation.

Health Status Assessment

Disease-specific and generic health status were assessed at baseline, and at 1, 6 and 12 months after enrollment using written questionnaires. Questionnaires were administered either during in-person visits to the study sites or by mail. Disease-specific health status was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ), a 23-item self-administered questionnaire that assesses specific health domains pertaining to heart failure: symptoms, physical limitation, social limitation, self-efficacy, and quality of life[6]. The individual domains can be combined into an overall summary score (KCCQ-OS), which was the pre-specified primary endpoint for this study. Values for all KCCQ domains and the summary score range from 0 to 100, with higher scores indicating less symptom burden and better quality of life. Prior studies have shown that the KCCQ-OS generally correlates with New York Heart Association functional class as follows: Class I: KCCQ-OS 75 to 100; Class II: 60 to 74; Class III: 45 to 59; Class IV: 0 to 44[7, 8]. Changes in the KCCQ-OS of 5, 10, and 20 points correspond to small, moderate or large clinical improvements, respectively[7]. The KCCQ has been shown to be a reliable, responsive and valid measure of symptoms, functional status and quality of life among a variety of patients with heart failure symptoms, including those with severe, symptomatic aortic stenosis[8].

Generic health status was evaluated with the Medical Outcomes Study Short-Form 12 (SF-12) questionnaire[9] and the EuroQOL (EQ-5D)[10]. Derived from the Short-Form 36, the SF-12 provides mental and physical summary scores that are scaled to overall US norms of 50 with standard deviations of 10. Higher scores indicate better quality of life, and the minimum clinically important difference for the SF-12 summary scores is 2 to 2.5 points[11]. The EQ-5D is a generic health status measure consisting of 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), which can be converted to utilities using an algorithm developed for the U.S. population[12]. Utilities are preference-weighted health status assessments with scores that range from 0 to 1, with 1 representing perfect health and 0 corresponding to the worst imaginable health state[13].

Statistical Analysis

At each follow-up time-point, scores for each of the disease-specific and generic health status scores were compared with baseline values using paired *t*-tests. At each time-point, the baseline value comparator consisted of only those patients that had a quality of life assessment performed at that time-point, thereby addressing survivor bias caused by attrition of sicker patients over time.

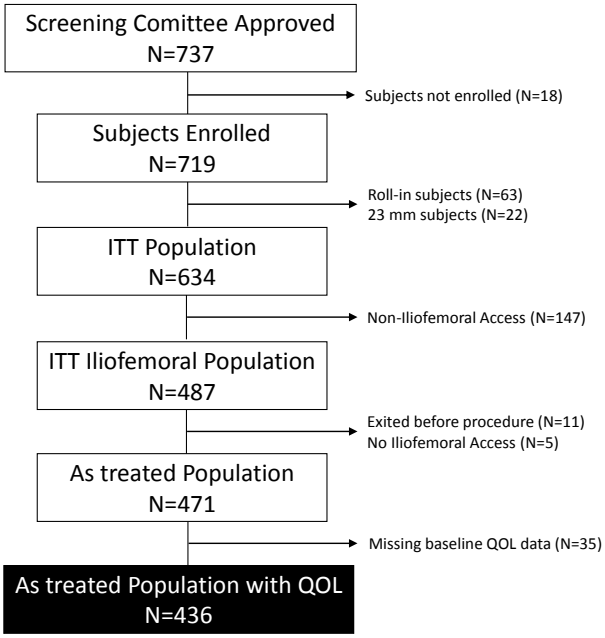

Figure 1. Patient Flow Chart
Consort diagram showing patient flow for the CoreValve U.S. Pivotal trial. The black box indicates the primary analytic population for this quality of life study.

To provide additional insight into the changes in health status over time, we also performed several categorical analyses. First, among the survivors at each time-point, we calculated the proportion of patients who had a moderate (≥10 points) or large (≥20 points) improvement in the KCCQ-OS compared with baseline. Second, we calculated the proportion of enrolled patients at each time-point with *favorable* and *excellent outcomes*, defined as being both alive and having a moderate or large improvement, respectively, in the KCCQ-OS compared with baseline. For these latter metrics, death was considered to be the same as failure to improve by the specified amount. The 95% confidence interval for proportion was based on the binomial distribution.

Finally, we calculated the proportion of patients with a poor outcome at 6 months after TAVR. For this analysis, a poor outcome was defined as any of the following at 6 months after TAVR: (1) death; (2) KCCQ-OS <45; or (3) decrease of ≥10 points on the KCCQ-OS from baseline[14]. We then used multivariable logistic regression to identify pre-procedural factors associated with poor 6-month outcome. Candidate variables for this analysis are listed in Supplementary Table 1. We used stepwise selection to identify variables associated with poor outcome at a significance level of $p \leq 0.10$, and then refit the model with the identified variables. The baseline score on the KCCQ-OS was forced into the model.

Table 1. Baseline Characteristics of the CoreValve Extreme Risk Cohort

	"As Treated" Population n=436
Socio-demographic characteristics	
Age, y	84.0 ± 8.5
Male	49.1% (214/436)
White Race	95.6% (417/436)
Body Mass Index, kg/m^2	28.6 ± 7.0
Clinical characteristics	
STS Risk Score	10.4 ± 5.6
STS: <5	12.6% (55/436)
STS: 5 - <10	42.7% (186/436)
STS: 10 - <15	26.1% (114/436)
STS: ≥15	18.6% (81/436)
Logistic EuroSCORE	22.8 ± 17.7
NYHA Class	
II	8.3% (36/434)
III	65.0% (282/434)
IV	26.7% (116/434)
Prior MI	31.7% (138/436)
Prior CABG	40.6% (177/436)
Prior Stroke	13.8% (60/436)
Home Oxygen	29.8% (130/436)
Chronic Kidney Disease	13.2% (57/431)
Mean Aortic Valve Gradient, mmHg	47.6 ± 14.8
Frailty and Disability Measures	
Albumin <3.3 g/dl	17.6% (75/427)
Wheelchair Bound	15.8% (69/436)
6-Minute Walk Distance, meters	167.5 ± 117
5-Meter Gait Speed > 6 seconds	84.5% (262/310)
Low Grip Strength*	65.7% (286/435)
Charlson Comorbidity Index	
Mild (1-2)	8.7% (38/436)
Moderate (3-4)	32.8% (143/436)
Severe (5)	58.5% (255/436)
Quality-of-Life Measures	
KCCQ overall summary	37.9 ± 22.2
75-100, %	7.1% (31/436)
60-74, %	9.6% (42/436)
45-59, %	18.8% (82/436)
0-45, %	64.4% (281/436)

Table 1. Baseline Characteristics of the CoreValve Extreme Risk Cohort (*continued*)

	"As Treated" Population n=436
KCCQ symptoms	48.1 ± 24.2
KCCQ physical limitation	35.3 ± 24.9
KCCQ social limitation	30.5 ± 28.4
KCCQ quality-of-life	36.3 ± 24.5
SF-12 physical summary score	28.5 ± 8.3
SF-12 mental summary score	45.8 ± 12.3
EQ-5D	0.65 ± 0.24

EQ-5D, European Quality of Life Group instrument-5 dimensions; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; MI, myocardial infarction; SF-12, Short Form-12 General Health Survey; STS, Society of Thoracic Surgeons; QOL, quality-of-life.* defined according to the thresholds proposed by Luna-Heredia et al.[24]

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC). A 2-sided *p*-value <0.05 was considered statistically significant with no correction for multiple comparisons.

RESULTS

Patient Population

Between February 2011 and August 2012, 737 patients with severe symptomatic aortic stenosis at extreme surgical risk from 41 U.S. sites were approved by the trial screening committee for inclusion in the CoreValve U.S. Extreme Risk Study. Of these, 18 were not enrolled (due to withdrawal by the patient or treating physician), 85 were roll-in patients or were treated in a separate registry with the 23 mm CoreValve, and 147 were planned for non-iliofemoral access, leaving 487 patients in the intention-to-treat population. Sixteen patients subsequently did not undergo iliofemoral TAVR, and an additional 35 did not have baseline health status data. With the exception of being somewhat younger, patients with missing baseline health status assessments were generally similar to those patients with complete baseline data (Supplementary Table 2). As such, the analytic population for our study included 436 patients who underwent iliofemoral TAVR and had baseline health status assessment (Figure 1).

The baseline characteristics of these patients are summarized in Table 1. The mean age was 84 years, and 49% were male. The mean aortic valve gradient was 48 mmHg, and 92% were classified as NYHA Class III-IV. The patients had a high burden of chronic medical conditions, including 30% who were on home oxygen and 16% who were wheel-

Table 2. Mean Follow-up Scores and Changes in Disease-Specific and Generic Health Status Measures Compared with Baseline

Scale/Time Point	Mean (±SD) Value	Mean Δ vs. Baseline	95% CI	*p*-value
KCCQ summary				
1 month	62.0 ± 25.8	23.9	(20.3, 27.5)	<0.001
6 months	67.6 ± 24.2	27.4	(24.2, 30.6)	<0.001
12 months	68.5 ± 23.6	27.4	(24.1, 30.8)	<0.001
KCCQ total symptoms				
1 month	69.0 ± 23.8	22.1	(18.6, 25.7)	<0.001
6 months	73.6 ± 23.1	23.0	(19.8, 26.2)	<0.001
12 months	74.2 ± 21.4	22.8	(19.5, 26.1)	<0.001
KCCQ physical limitations				
1 month	53.2 ± 30.7	16.5	(12.0, 21.0)	<0.001
6 months	57.5 ± 28.7	19.4	(15.5, 23.3)	<0.001
12 months	53.7 ± 28.6	14.1	(9.9, 18.2)	<0.001
KCCQ social limitation				
1 month	58.5 ± 33.7	24.8	(19.6, 29.9)	<0.001
6 months	63.8 ± 31.2	27.2	(22.4, 32.1)	<0.001
12 months	64.7 ± 31.0	29.1	(23.8, 34.4)	<0.001
KCCQ quality of life				
1 month	64.7 ± 28.1	28.9	(24.7, 33.0)	<0.001
6 months	72.0 ± 26.7	33.7	(30.0, 37.4)	<0.001
12 months	74.8 ± 25.0	36.3	(32.5, 40.1)	<0.001
SF-12 physical				
1 month	35.0 ± 10.2	5.8	(4.4, 7.2)	<0.001
6 months	33.6 ± 11.3	5.0	(3.5, 6.4)	<0.001
12 months	34.1 ± 10.6	5.1	(3.7, 6.5)	<0.001
SF-12 mental				
1 month	49.7 ± 12.3	3.9	(1.9, 5.8)	<0.001
6 months	51.4 ± 11.1	4.5	(2.7, 6.3)	<0.001
12 months	51.7 ± 11.8	5.1	(3.3, 7.0)	<0.001
EQ-5D utility				
1 month	0.726 ± 0.238	0.084	(0.047, 0.121)	<0.001
6 months	0.757 ± 0.202	0.092	(0.065, 0.120)	<0.001
12 months	0.727 ± 0.208	0.058	(0.027, 0.090)	0.003

CI indicates confidence interval; EQ-5D KCCQ, Kansas City Cardiomyopathy Questionnaire; and SF-12, Short-Form-12 General Health Survey. **p*-value derived from paired *t*-tests comparing follow-up score and baseline.

chair bound. Both disease-specific and generic health status measures demonstrated substantial impairment at baseline. The mean KCCQ-OS score was 37.9 ± 22.2 (roughly comparable to New York Heart Association Class IV); the mean SF-12 physical summary score was 28.5 ± 8.3 (~2 SD below the standard for the general U.S. population); the mean SF-12 mental summary score was 45.8 ± 12.3; and the mean baseline EQ-5D score was 0.65 ± 0.24.

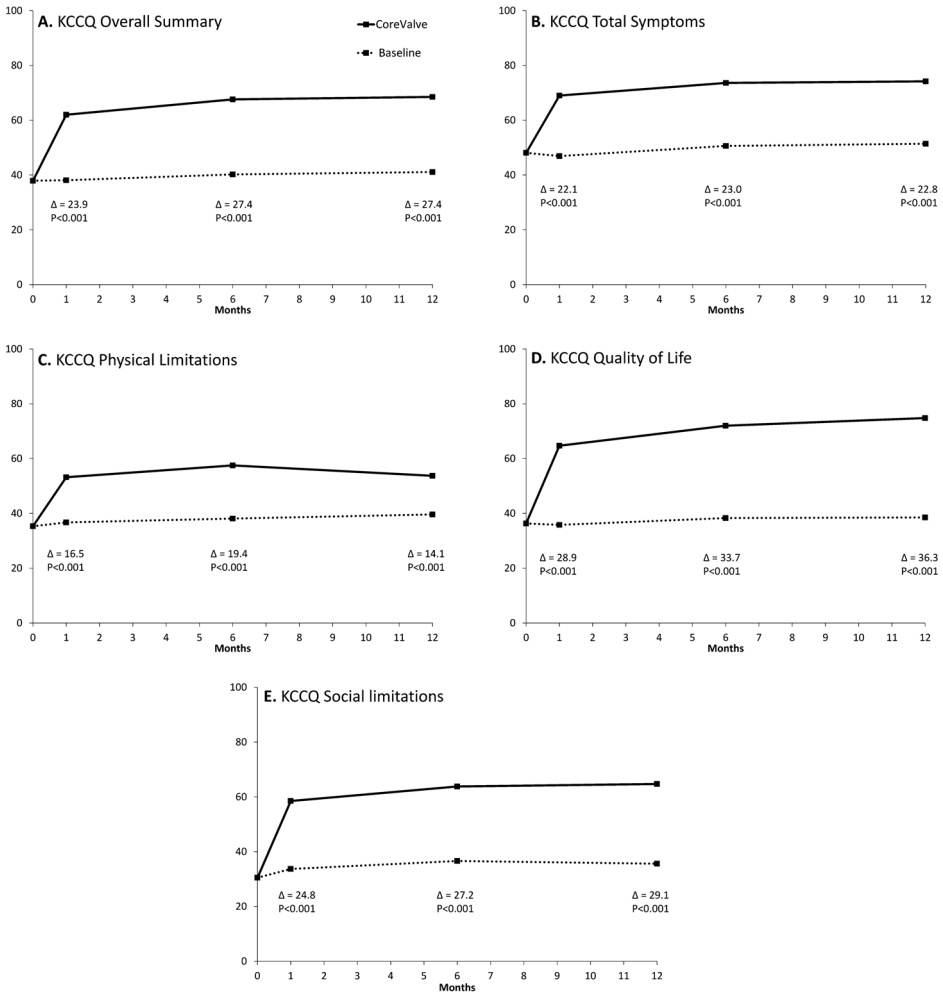

Figure 2. Disease-specific Health Status after TAVR

Changes in disease-specific health status according to the KCCQ overall summary scale (panel A) and subscales (panels B-E) at 1, 6, and 12 months after TAVR. Baseline values indicated by the dashed line correspond to the evaluable patient population at each time point. Mean values and *p*-values are derived from paired *t*-tests comparing each patient with his or her own baseline value. TAVR, transcatheter aortic valve replacement.

Follow-up Health Status

Follow-up health status data were available for 58% of surviving patients at 1 month, 74% at 6 months, and 77% at 12 months after TAVR. Mean scores and the mean changes from baseline at each follow-up time-point are summarized in Table 2 and Figure 2. On average, KCCQ-OS scores increased by 23.9 points at 1 month and 27.4 points at 6 and 12 months after TAVR compared with baseline ($p < 0.001$ for all comparisons). The individual KCCQ subscales showed similar patterns (Table 2, Figure 2). The SF-12 physical and mental summary scores improved by ~5 points at 6 and 12 months compared with baseline, and EQ-5D utility values also increased substantially at all time-points as well ($p < 0.003$ for all comparisons; Table 2, Figure 3).

Categorical Analyses

The rates of moderate and large improvements in KCCQ-OS and favorable and excellent outcomes at each time-point are shown in Table 3. Among responders to the surveys, the proportion of patients with large KCCQ-OS improvements was 58% at 1 month and 59% at 12 months after TAVR. The proportion of treated patients with an excellent outcome

Table 3. Proportion of Patients with Clinically Important Improvement in the KCCQ Summary Score

Population and Level of Benefit	Proportion (95% CI) [n/N]
Among responders to the survey	
Moderate improvement (≥10-point increase from baseline)	
1 month	70.0% (63.9, 75.6) [175/250]
6 months	71.1% (65.3, 76.4) [192/270]
12 months	71.3% (65.3, 76.7) [181/254]
Large improvement (≥20-point increase from baseline)	
1 month	58.0% (51.6, 64.2) [145/250]
6 months	61.1% (55.0, 67.0) [165/270]
12 months	59.1% (52.7, 65.1) [150/254]
Among all treated patients*	
Favorable outcome (alive with ≥10-point increase from baseline)*	
1 month	62.3% (56.3, 68.0) [175/281]
6 months	54.9% (49.5, 60.1) [192/350]
12 months	49.5% (44.2, 54.7) [181/366]
Excellent outcome (alive with ≥20-point increase from baseline)*	
1 month	51.6% (45.6, 57.6) [145/281]
6 months	47.1% (41.8, 52.5) [165/350]
12 months	41.0% (35.9, 46.2) [150/366]

*Denominator includes patients who died but excludes patients who voluntarily withdrew from the study before the time point.
KCCQ, Kansas City Cardiomyopathy Questionnaire.

(i.e., alive with a large improvement in KCCQ-OS) was 52% at 1 month and 41% at 12 months after TAVR.

Factors Associated with Poor Outcome

The proportion of patients with a poor outcome was 39% at 6 months (22% death, 16% very poor quality of life, and 1.4% quality of life decline). Pre-procedural factors that were independently associated with a poor outcome are shown in Table 4. Patients who were wheelchair-bound were 2.6 times more likely to have a poor outcome after TAVR, compared with patients who were able to ambulate (95% CI, 1.3-5.2). In addition, having a lower aortic valve gradient, previous CABG, and requiring home oxygen were strongly associated with a poor outcome. The association between the STS risk score (i.e., the predicted risk of operative mortality with surgical AVR) and a poor outcome of TAVR was only significant for an STS mortality risk >15%. When patients were compared according to whether they met VARC criteria for procedural success[15], those patients who achieved procedural success had greater improvements in health status (mainly at the

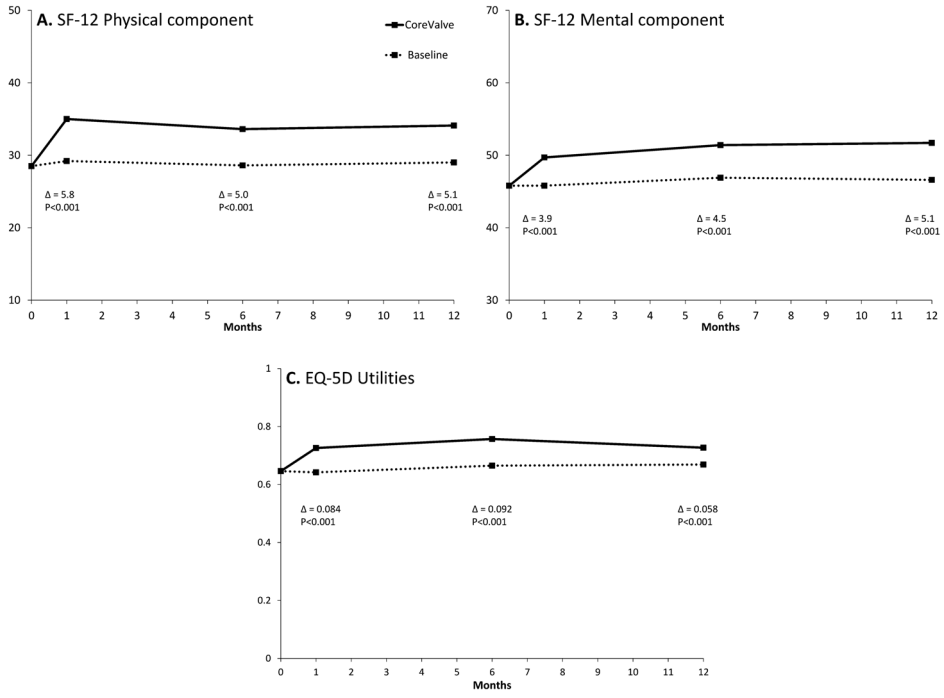

Figure 3. Generic Health Status after TAVR
Changes in generic health status according to the SF-12 and EQ-5D at 1, 6, and 12 months after TAVR. Baseline values indicated by the dashed line correspond to the evaluable patient population at each time point. Mean values and *p*-values are derived from paired *t*-tests comparing each patient with his or her own baseline value. TAVR, transcatheter aortic valve replacement.

Table 4. Predictors of Poor Outcome*

Predictor	OR (95% CI)	*p*-value
Baseline KCCQ overall score	1.0 (1.0, 1.0)	0.488
Prior CABG	1.9 (1.2, 3.3)	0.011
Mean aortic valve gradient (per 10 mmHg)**	0.8 (0.7, 0.9)	0.007
STS Score***		0.052
STS 10-15	1.1 (0.6, 2.2)	
STS ≥15	2.0 (1.1, 3.7)	
Home oxygen	1.7 (1.0, 3.0)	0.044
Albumin <3.3 g/dl	1.8 (0.9, 3.5)	0.073
Wheelchair Bound	2.6 (1.3, 5.2)	0.006

* Poor outcome defined as 1) Death within 6 months; 2) KCCQ-OS < 45; or 3) KCCQ-OS decrease more than 10 points vs. baseline.
** Resting gradient
*** Reference category is STS mortality risk score <10
Model C-statistic = 0.72

1 month time point) and were more likely to experience favorable or excellent outcomes at all timepoints (Supplementary Tables 3 and 4). After adjusting for those pre-procedure factors summarized in Table 4, procedural success was inversely associated with a poor outcome after TAVR (adjusted odds ratio 0.40, $p < 0.001$).

DISCUSSION

The CoreValve U.S. Extreme Risk Study has demonstrated that TAVR using a self-expanding bioprosthesis is safe and effective in patients with symptomatic severe aortic stenosis at prohibitive risk for surgical replacement[5]. In this pre-specified quality of life sub-study, we found that among patients at prohibitive risk of surgical complications, treatment with the CoreValve device via a transfemoral approach leads to substantial improvement in disease-specific and general health status. These benefits were evident by 1 month after TAVR and were followed by modest additional improvement through 12 months. In addition, we identified several factors, including comorbid conditions, disability/frailty, and valve physiology, that were independently associated with poor outcomes after TAVR—a finding which, if replicated in future studies, may help to inform clinical decision-making in patients considering TAVR.

We observed substantial improvements in both disease-specific and generic health status measures after TAVR. Among surviving patients, the mean improvements in the KCCQ-OS scale were >20 points at all follow-up time-points; in previous studies, a 5-point change in this scale has been found to be clinically meaningful and also cor-

relates with important differences in survival and health care costs[16, 17]. Furthermore, we observed increases in SF-12 physical and mental component scores of ~5 points. This increment represents twice the minimum clinically important difference for an individual patient[11] and is roughly comparable to reversing 10 years of normal decline in health in the general population[18].

Previous studies have also reported substantial improvements in health status after surgical AVR[19, 20] and TAVR[3, 21-23]. However, most of these studies have only examined changes in generic health status. To date, only one other multicenter trial, the Placement of AoRTic TraNscathetER Valve (PARTNER) trial, has rigorously evaluated disease-specific health status after TAVR[3, 23]. In PARTNER Cohort B, which included patients who were considered surgically inoperable (i.e. similar to the CoreValve Extreme Risk U.S, trial), TAVR resulted in substantial improvement in both disease-specific and generic health status. Although cross-trial extrapolation should be considered purely exploratory, the health status outcomes observed in the CoreValve Extreme Risk and PARTNER B trials were roughly comparable with respect to both disease-specific and generic health status measures through the first year of follow-up (Supplementary Table 5). The current study thus confirms that the health status benefits of TAVR are not restricted solely to balloon-expandable transcatheter valves but also apply to the CoreValve self-expanding transcatheter valve.

Although many patients have excellent outcomes after TAVR, we also found that nearly 40% of patients did not experience meaningful improvements in survival or functional status at 6 months after TAVR. We identified pre-operative factors that are associated with poor outcomes, which included measures of disability and frailty (e.g., wheelchair dependency, low serum albumin), comorbidity (prior CABG, extremely high predicted surgical mortality, oxygen dependency) and valve physiology (mean aortic valve gradient). Compared with prior work investigating predictors of poor outcome after TAVR in the PARTNER population (both inoperable and high risk patients) we found some similar predictors (e.g. poor functional status, oxygen dependence, low aortic valve gradient) and some novel predictors (e.g. low albumin, prior bypass surgery) in the CoreValve population[14]. Further work is needed to establish a model that can be applied across all TAVR patients, regardless of valve type and surgical risk, such that patients at high-risk for poor outcomes may be identified prospectively. In the future, this information could be invaluable to both patients and physicians, to help them decide whether or not to undergo TAVR and also to set realistic expectations for recovery.

Our study has several potential limitations. First and foremost, the CoreValve U.S. Extreme Risk Study was a single-arm trial, and as such, there was no control arm to which the results of TAVR could be compared. Originally, the study design intended to randomize

patients CoreValve implantation vs. medical therapy. However, after publication of the results from Cohort B of the PARTNER trial[2], the investigators and the FDA felt that it was no longer ethical to randomize these patients to standard therapy. Consequently, we were limited to comparing health status after TAVR with each patient's individual baseline. Of note, the control arm of the PARTNER B trial, which enrolled a similar patient population, demonstrated modest short-term improvements in health status (most likely attributable to the high rate of balloon aortic valvuloplasty) that were not sustained at 1-year[3]. Second, the proportion of patients with missing quality of life data increased modestly over time due to both mortality and non-response among surviving patients. To address this issue, we also reported categorical outcome variables that included all treated patients (as opposed to responding patients; i.e., excellent outcome), thereby treating patients with missing data (including death) as 'treatment failures'. If sicker patients were less likely to respond, we may have overestimated the extent of clinical benefit. Third, our study was restricted to the iliofemoral cohort of the CoreValve extreme risk trial and included only 12 months of follow-up. Thus, the durability of the observed health status improvements, as well as the health status improvement after non-iliofemoral procedures remain unknown.

Conclusions

In patients with severe symptomatic aortic stenosis who are at extreme risk of surgical complications, TAVR using the CoreValve self-expanding aortic bioprosthesis via a transfemoral approach resulted in large improvements in both disease-specific and generic health status measures in the majority of surviving patients. Nonetheless, similar to prior studies with a balloon expandable transcatheter valve, there remains a substantial minority of patients who do not derive a meaningful survival or quality of life benefit from TAVR. A combination of pre-procedural clinical, frailty, disability. and physiologic factors may provide further insight into identifying patients at high-risk for poor outcomes.

ACKNOWLEDGEMENTS

We thank Holly Vitense and Jane Moore for their administrative assistance.

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APPENDIX

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Supplementary Table 1. Variables considered for the Multivariable Logistic Regression Model

Baseline KCCQ-OS Score
Age
Male
COPD (None/Mild/Moderate/Severe)
Severe vs. None
Moderate vs. None
Mild vs. None
Diabetes
Prior stroke
Renal failure
Prior CABG
Prior Myocardial Infarction
Peripheral Vascular Disease
Moderate/Severe mitral regurgitation
Left Ventricular Ejection Fraction
Mean aortic valve gradient
Logistic EuroSCORE
STS Risk Score (<10, 10-15, ≥15)
STS ≥15 vs. STS <10
STS 10-15 vs. STS <10
Home Oxygen
Charlson Comorbidity Score
score 5 or more vs. score 1/2
score 3/4 vs. score 1/2
Albumin <3.3
5-meter Gait Speed >6 seconds
6-minute Walk Test
Grip Strength < Threshold
Katz 'Activities of Daily Living >0
Mini-Mental Status Exam <25
Wheelchair Bound

Supplementary Table 2. Comparison of Baseline Characteristics among Patients with or without Baseline Health Status Data

	Patients with baseline health status data (n=436)	Patients without baseline health status data (n=35)	*p*-value
Socio-demographic characteristics			
Age	84.0 ± 8.5	80.3 ± 8.8	0.014
Male	49.1% (214/436)	48.6% (17/35)	0.954
White	95.6% (417/436)	91.4% (32/35)	0.219
BMI	28.6 ± 7.0	29.5 ± 8.2	0.454
Clinical characteristics			
STS Risk Score	10.4 ± 5.6	8.7 ± 4.6	0.088
STS Risk Score Category			0.624
STS: <5	12.6% (55/436)	20.0% (7/35)	
STS: 5 - <10	42.7% (186/436)	42.9% (15/35)	
STS: 10 - <15	26.1% (114/436)	22.9% (8/35)	
STS: >=15	18.6% (81/436)	14.3% (5/35)	
Logistic EuroSCORE	22.8 ± 17.7	20.5 ± 12.5	0.452
NYHA Class			0.391
II	8.3% (36/434)	14.7% (5/34)	
III	65.0% (282/434)	61.8% (21/34)	
IV	26.7% (116/434)	23.5% (8/34)	
Prior MI	31.7% (138/436)	25.7% (9/35)	0.466
Prior CABG	40.6% (177/436)	40.0% (14/35)	0.945
Previous Stroke	13.8% (60/436)	11.4% (4/35)	1.000
Home oxygen	29.8% (130/436)	37.1% (13/35)	0.364
Chronic kidney disease	13.2% (57/431)	5.7% (2/35)	0.290
Mean aortic valve gradient	47.6 ± 14.8	45.0 ± 14.0	0.324
Frailty and disability measures			
Albumin<3.3g/dL	17.6% (75/427)	16.7% (5/30)	0.900
Wheelchair bound	15.8% (69/436)	28.6% (10/35)	0.052
6 minute walk test	167.5 ± 117.0	218.2 ± 152.7	0.164
5 meter gait speed>6 secs	84.5% (262/310)	75.0% (9/12)	0.413
Grip strength < threshold*	65.7% (286/435)	85.7% (30/35)	0.015
Charlson comorbidity score			0.928
Mild (score 1,2)	8.7% (38/436)	5.7% (2/35)	
Moderate (score 3,4)	32.8% (143/436)	34.3% (12/35)	
Severe (score 5)	58.5% (255/436)	60.0% (21/35)	

NYHA, New York Heart Association; MI, myocardial infarction; STS, Society of Thoracic Surgeons; * defined according to the thresholds proposed by Luna-Heredia et al.[24]

Supplementary Table 3. Mean Follow-up Scores and Changes in Health Status Compared with Baseline, Stratified According to Procedural Success

Scale/Time Point	Patients with procedural success			Patients without procedural success			Adjusted difference between successful vs. unsuccessful procedures *	
	Mean ±SD	Mean Δ vs. Baseline (95% CI)	*p*-value	Mean ±SD	Mean Δ vs. Baseline (95% CI)	*p*-value	Difference (95% CI)	*p*-value
KCCQ summary								
1 month	63.6 ± 25.6	26.5 (22.6, 30.4)	<0.001	55.1 ± 26.8	12.2 (2.7, 21.6)	0.013	10.9 (2.5, 19.4)	0.012
6 months	67.0 ± 24.6	27.7 (24.1, 31.3)	<0.001	69.6 ± 22.9	28.4 (21.9, 34.8)	<0.001	−1.9 (−9.3, 5.6)	0.622
12 months	68.6 ± 23.3	28.5 (24.9, 32.1)	<0.001	66.6 ± 25.4	24.3 (16.0, 32.7)	<0.001	2.5 (−5.0, 10.1)	0.508
KCCQ total symptoms								
1 month	69.4 ± 24.0	24.0 (20.1, 27.8)	<0.001	66.2 ± 23.9	12.8 (3.2, 22.4)	0.010	5.4 (−2.4, 13.2)	0.175
6 months	72.7 ± 23.4	24.2 (20.6, 27.7)	<0.001	76.8 ± 22.2	19.5 (12.7, 26.3)	<0.001	−1.0 (−8.0, 6.1)	0.790
12 months	73.8 ± 21.2	24.7 (21.1, 28.3)	<0.001	73.4 ± 22.2	14.5 (7.1, 22.0)	<0.001	3.3 (−3.6, 10.2)	0.354
KCCQ physical limitations								
1 month	55.4 ± 29.7	19.7 (14.8, 24.6)	<0.001	43.4 ± 32.7	−0.9 (−11.3, 9.6)	0.866	17.6 (6.9, 28.4)	0.001
6 months	56.3 ± 28.7	19.5 (15.0, 23.9)	<0.001	59.5 ± 28.5	20.1 (11.8, 28.4)	<0.001	−2.7 (−12.2, 6.8)	0.579
12 months	53.4 ± 27.9	15.1 (10.5, 19.6)	<0.001	51.3 ± 30.3	10.8 (1.0, 20.6)	0.032	2.2 (−7.3, 11.8)	0.641
KCCQ social limitation								
1 month	60.5 ± 32.9	27.9 (22.5, 33.2)	<0.001	47.8 ± 36.7	9.0 (−7.4, 25.4)	0.272	15.5 (3.0, 28.1)	0.015
6 months	63.6 ± 31.7	27.7 (22.3, 33.1)	<0.001	62.8 ± 31.1	26.0 (15.0, 37.0)	<0.001	1.7 (−9.4, 12.9)	0.757
12 months	64.5 ± 30.8	29.6 (23.7, 35.4)	<0.001	63.1 ± 32.0	28.4 (16.1, 40.7)	<0.001	−1.3 (−12.4, 9.7)	0.816
KCCQ quality of life								
1 month	66.0 ± 27.8	31.0 (26.6, 35.4)	<0.001	58.8 ± 30.8	19.0 (6.2, 31.8)	0.005	9.3 (−0.4, 19.1)	0.061
6 months	71.7 ± 27.4	33.6 (29.4, 37.7)	<0.001	74.2 ± 23.2	36.7 (28.8, 44.7)	<0.001	−2.8 (−11.1, 5.6)	0.515
12 months	75.3 ± 25.5	37.0 (32.7, 41.2)	<0.001	74.1 ± 23.9	35.7 (27.1, 44.3)	<0.001	0.8 (−7.5, 9.2)	0.843

Supplementary Table 3. Mean Follow-up Scores and Changes in Health Status Compared with Baseline, Stratified According to Procedural Success (*continued*)

Scale/Time Point	Patients with procedural success			Patients without procedural success			Adjusted difference between successful vs. unsuccessful procedures *	
	Mean ±SD	Mean Δ vs. Baseline (95% CI)	*p*-value	Mean ±SD	Mean Δ vs. Baseline (95% CI)	*p*-value	Difference (95% CI)	*p*-value
SF-12 physical								
1 month	35.5 ± 10.4	6.2 (4.6, 7.7)	<0.001	31.9 ± 9.4	4.1 (−0.1, 8.2)	0.056	2.7 (−1.0, 6.5)	0.153
6 months	33.7 ± 11.4	5.0 (3.3, 6.6)	<0.001	34.0 ± 11.7	5.8 (2.6, 9.0)	<0.001	−0.6 (−4.3, 3.1)	0.762
12 months	34.4 ± 10.7	5.3 (3.7, 6.9)	<0.001	31.7 ± 10.9	4.8 (1.0, 8.5)	0.014	1.6 (−2.0, 5.3)	0.376
SF-12 mental								
1 month	50.3 ± 11.6	4.7 (2.7, 6.8)	<0.001	45.7 ± 15.8	−0.4 (−6.5, 5.6)	0.882	4.5 (−0.1, 9.1)	0.058
6 months	51.4 ± 11.0	5.0 (3.0, 7.1)	<0.001	50.1 ± 12.1	2.9 (−0.8, 6.5)	0.121	1.7 (−2.1, 5.4)	0.389
12 months	51.0 ± 12.2	5.1 (3.0, 7.2)	<0.001	53.2 ± 10.5	6.0 (1.4, 10.5)	0.011	−1.7 (−5.9, 2.5)	0.434
EQ-5D utility								
1 month	0.748 ± 0.227	0.111 (0.072, 0.151)	<0.001	0.630 ± 0.261	−0.035 (−0.139, 0.069)	0.500	0.129 (0.051, 0.207)	0.001
6 months	0.759 ± 0.198	0.102 (0.071, 0.132)	<0.001	0.728 ± 0.223	0.049 (−0.007, 0.105)	0.084	0.032 (−0.027, 0.092)	0.282
12 months	0.725 ± 0.205	0.067 (0.032, 0.102)	<0.001	0.700 ± 0.250	0.011 (−0.061, 0.083)	0.759	0.037 (−0.034, 0.107)	0.305

CI indicates confidence interval; EQ-5D KCCQ, Kansas City Cardiomyopathy Questionnaire; and SF-12, Short-Form-12 General Health Survey. *Study sites were treated as random effects in the mixed model.

Supplementary Table 4. Proportion of Patients with Clinically Important Improvement in the KCCQ Overall Summary Score According to Procedural Success

Population and Level of Benefit	Patients with procedural success	Patients without procedural success	*p*-value**
	Proportion (95% CI) [n/N]	Proportion (95% CI) [n/N]	
Among responders to the survey			
Moderate improvement (≥10-point increase from baseline)			
1 month	73.1% (67.0%, 79.1%) (152/208)	55.3% (39.5%, 71.1%) (21/38)	0.027
6 months	70.7% (64.7%, 76.7%) (157/222)	75.0% (62.2%, 87.8%) (33/44)	0.566
12 months	72.7% (66.7%, 78.8%) (152/209)	65.9% (51.3%, 80.4%) (27/41)	0.372
Large improvement (≥20-point increase from baseline)			
1 month	61.5% (54.9%, 68.2%) (128/208)	44.7% (28.9%, 60.5%) (17/38)	0.053
6 months	60.8% (54.4%, 67.2%) (135/222)	63.6% (49.4%, 77.9%) (28/44)	0.725
12 months	59.3% (52.7%, 66.0%) (124/209)	58.5% (43.5%, 73.6%) (24/41)	0.925
Among all treated patients*			
Favorable outcome (alive with ≥10-point increase from baseline)*			
1 month	72.0% (66.0%, 78.1%) (152/211)	34.4% (22.5%, 46.3%) (21/61)	< 0.001
6 months	60.6% (54.7%, 66.6%) (157/259)	42.3% (31.3%, 53.3%) (33/78)	0.004
12 months	56.5% (50.6%, 62.4%) (152/269)	33.3% (23.1%, 43.6%) (27/81)	< 0.001
Excellent outcome (alive with ≥20-point increase from baseline)*			
1 month	60.7% (54.1%, 67.3%) (128/211)	27.9% (16.6%, 39.1%) (17/61)	< 0.001
6 months	52.1% (46.0%, 58.2%) (135/259)	35.9% (25.3%, 46.5%) (28/78)	0.012
12 months	46.1% (40.1%, 52.1%) (124/269)	29.6% (19.7%, 39.6%) (24/81)	0.009

*Denominator includes patients who died but excludes patients who voluntarily withdrew from the study before the time point.

KCCQ, Kansas City Cardiomyopathy Questionnaire. ***P* comparing proportions of good outcomes in successful vs. unsuccessful procedures.

Supplementary Table 5. Comparison of 12-month Health Status Outcomes between the CoreValve Extreme Risk and PARTNER B Trials

Scale	CoreValve Extreme Risk	PARTNER B
12 month Δ vs. Baseline		
KCCQ summary	27.4	31.8
KCCQ total symptoms	22.8	26.2
KCCQ physical limitations	14.1	16.8
KCCQ quality of life	36.3	41.2
SF-12 physical	5.1	6.6
SF-12 mental	5.1	7.0
Favorable outcome (alive with ≥10-point increase from baseline)*		
12 months	49.5%	47.5%
Excellent outcome (alive with ≥20-point increase from baseline)*		
12 months	41.0%	38.0%

* Denominator includes patients who died but excludes patients who voluntarily withdrew from the study before the time point.

CHAPTER 7

Costs for Surgical Aortic Valve Replacement According to Pre-operative Risk Categories

Osnabrugge RL, Speir AM, Head SJ, Fonner CE, Fonner E Jr, Ailawadi G, Kappetein AP, Rich JB.

Ann Thorac Surg. 2013;96:500-6.

ABSTRACT

Introduction

The introduction of transcatheter aortic valve replacement (TAVR) has led to more rigorous evaluation of surgical aortic valve replacement (SAVR) as a benchmark for TAVR. However, limited real-life cost data of SAVR are available. Therefore, the purpose or our study was to assess actual costs and resource utilization of SAVR in patients at different operating risk.

Methods

Study data were drawn from a multi-institutional statewide database comprised of all cardiac surgical procedures in the Commonwealth of Virginia. The current study included 2,530 elective, primary, isolated SAVRs performed from 2003 to 2012. Clinical data were matched with universal billing data. Cost-to-charge ratios were applied, and price indices were used to convert all costs to 2012 U.S. dollars. Patients were stratified into low, intermediate and high risk categories according to STS-PROM score: 0-4%, 4-8% and >8%, respectively. Clinical outcomes, resource use, and costs were compared between categories.

Results

Mean total costs for the overall cohort were $37,559 ± 27,557. There was an increase in mean total costs from the low (n = 2,002) to intermediate (n = 415) to high (n = 113) risk category ($35,021 ± 22,642 versus $46,101 ± 42,460 versus $51,145 ± 31,655; $p < 0.001$). With increasing risk, there were higher rates of post-operative mortality (low 1.2% versus intermediate 2.7% versus high 6.2%, $p < 0.001$) and stroke (1.0% versus 2.4% versus 2.7%; $p = 0.37$). The proportion of patients with any post-operative complication was higher with increasing risk (34% versus 48% versus 53%; $p < 0.001$). Length of stay increased from 6.8 days in the low risk category to 10.2 and 11.3 days in the intermediate and high risk category, respectively ($p < 0.001$).

Conclusions

Higher STS-PROM was significantly associated with higher costs, post-operative mortality, complications, and length of stay. The SAVR cost data in the intermediate and high risk category provide a basis for the analysis of TAVR cost-effectiveness.

INTRODUCTION

The standard treatment for patients with symptomatic severe aortic stenosis (AS) is surgical aortic valve replacement (SAVR). Approximately 67,500 SAVR procedures are performed annually in the United States.[1, 2] As the population is aging, the prevalence of AS and consequently the utilization of SAVR are expected to increase.

Transcatheter aortic valve replacement (TAVR) is a less-invasive treatment in patients at high or prohibitive surgical risk.[3, 4] In the recent randomized PARTNER trial, TAVR was associated with similar clinical outcomes and a small quality-of-life gain as compared with SAVR in high risk patients.[5-7] Therefore and due to the fact that health care expenditure outpace the growth of the economy, costs have become a crucial factor in the decision-making in patients with AS at high risk.[8] However, little is known about the costs of SAVR in everyday practice.

We therefore sought to assess the costs and resource use of SAVR stratified on the Society of Thoracic Surgery Predicted Risk of Mortality (STS-PROM), thereby providing a benchmark for the cost of TAVR in current and future everyday practice.

METHODS

Study Population

The clinical records of patients undergoing cardiac surgery were prospectively collected in the Virginia Cardiac Surgery Quality Initiative (VCSQI) database. For this project, all elective isolated SAVRs between January 2003 and June 2012 were selected. Patients with infective endocarditis or previous valve surgery were excluded, leading to 2,562 eligible patients. After exclusion of 32 patients with data errors, 2,530 patients remained for analysis.

VCSQI is a voluntary consortium of 17 hospitals and 13 cardiac surgical centers providing cardiac surgery in the Commonwealth of Virginia.[9] Approximately 99% of all cardiac surgical procedures were captured in the database. VCSQI members contributed their data to The Society of Thoracic Surgeons (STS) Adult Cardiac Database. Each of VCSQI's hospital members agreed in advance to share data for secondary statistical analysis. Patient data are de-identified and aggregated for research purposes only. Business Associates Agreements are in place between VCSQI, its 17 member hospitals, and database vendor (Armus Corporation, San Mateo CA). Database retrievals and analyses conducted by VCSQI primarily for secondary analyses are not normally reviewed by hospital In-

stitutional Review Boards (IRBs). However, individual member hospitals are invited to circulate study prospectuses to their IRBs for review and exemption prior to launching specific quality improvement initiatives.

Clinical Data

Clinical data included all the data routinely collected in the STS database and post-operative outcomes included death, stroke, renal failure, atrial fibrillation, deep sternal wound infection, permanent stroke, prolonged ventilation and reoperations, all defined according to the STS database definitions.[10] Each institution was responsible for coding and submitting its data to VCSQI's repository and agreed on the data definitions, data collection and timely submission.

Cost Data

The process of combining clinical and financial data in the VCSQI database has been described elsewhere.[11] Briefly, STS patient records were matched with universal billing (UB) discharge records, which are used by institutional health care providers throughout the U.S. The UB-04 form replaced its predecessor UB-92 in 2007 and represents the patient's final hospital bill. Charges for all of the ICD-9 (International Classification of Diseases, 9th revision) revenue codes were grouped into 20 logical cost categories (see list in the Appendix). Subsequently, cost-to-charge ratios from each participating institution were applied to the costs in these 20 categories. The total costs estimate was the sum of all the 20 categories. The medical care service component of the U.S. consumer price index was used to convert all costs to U.S. dollars for the year 2012.[12]

Statistical Analysis

Patients were subdivided into low (STS-PROM<4), intermediate (STS-PROM 4-8) and high (STS-PROM>8) risk categories. The three categories were analyzed for differences in baseline characteristics, clinical outcomes, resource use and costs. Variables were tested for normality using the Kolmogorov-Smirnov test; normally distributed variables were compared between risk categories using one-way analysis-of-variance and for non-parametric distributions, the Kruskal-Wallis test was used. Pairwise post-hoc comparisons were done with Bonferroni correction, using *t*-tests for parametric distributions and Mann-Whitney U-tests for non-parametric distributions. Categorical variables were compared by the Pearson chi-square test. Cost and length of stay data are reported as both mean and median values and were compared using *t*-tests, which are appropriate given our focus on comparing mean costs between risk categories.[13] All analyses were performed using Excel 2010 (Microsoft, Redmond, Wash) and SPSS for Windows (version 20.0.0; SPSS, Chicago, Ill).

RESULTS

Patient Characteristics

Patient characteristics of the overall cohort and different risk categories are presented in Table 1. The low risk category consisted of 2,002 (79%) patients, the intermediate risk category of 415 (16%) patients and the high risk category of 113 (5%) patients. There was a significant difference in the mean STS-PROM score according to risk category: 1.8 ± 0.9, 5.4 ± 1.1 and 12.6 ± 4.3 in the low, intermediate, and high risk category, respectively. The cohort existed of elderly patients (67.4 ± 12.7 years), with significantly younger patients in the low risk category (64.6 ± 12.2 years) compared to the intermediate (77.7 ± 7.8 years) and high risk category (79.5 ± 7.3 years; $p < 0.001$). As expected, comorbidities were more prevalent in the higher risk categories.

Table 1. Patient Characteristics

	Overall Cohort (n=2,530)	Low risk (n=2,002)	Intermediate risk (n=415)	High risk (n=113)	*p*-value
Age, years	67.4 ± 12.7	64.6 ± 12.2	77.7 ± 7.8	79.5 ± 7.3	<0.001[a]
Female, n (%)	1054 (41.7)	788 (39.4)	212 (51.1)	54 (47.8)	<0.001[b]
STS-PROM, %	2.9 ± 2.8 (2.1)	1.8 ± 0.9 (1.7)	5.4 ± 1.1 (5.2)	12.6 ± 4.3 (11.1)	<0.001[a]
Body Mass Index, kg/m²	29.5 ± 6.7	30.0 ± 6.7	27.9 ± 6.5	27.4 ± 6.3	<0.001[b]
Creatinine, mg/dl	1.13 ± 0.85	1.03 ± 0.60	1.30 ± 1.13	2.26 ± 1.91	<0.001[a]
Caucasian	2206 (87.2)	1747 (88.8)	359 (88.6)	100 (89.3)	0.98
Ejection Fraction <30%	67 (2.6)	41 (2.0)	14 (3.4)	12 (10.6)	<0.001[c]
History of smoking	314 (12.4)	272 (13.6)	33 (8.0)	9 (8.0)	0.03[d]
Chronic Lung Disease	460 (18.2)	287 (14.3)	120 (28.9)	53 (46.9)	<0.001[a]
Hypertension	1823 (72.1)	1355 (67.7)	366 (88.2)	102 (90.3)	<0.001[b]
Diabetes	657 (26.0)	423 (21.1)	175 (42.2)	59 (52.2)	<0.001[b]
History renal failure	42 (3.1)	9 (0.8)	11 (6.4)	22 (27.5)	<0.001[a]
History of MI ≤7 days	153 (6.0)	65 (3.2)	60 (14.5)	28 (24.8)	<0.001[a]
NYHA class (III, IV)	754 (45.4)	483 (40.8)	194 (52.7)	77 (73.3)	<0.001[b]
Peripheral artery disease	204 (8.1)	82 (4.1)	73 (17.6)	49 (43.4)	<0.001[a]
Prior stroke	115 (8.9)	59 (2.9)	39 (13.8)	17 (23.3)	<0.001[a]
Cerebral vascular disease	310 (12.3)	178 (8.9)	91 (21.9)	41 (36.3)	<0.001[a]
Prior Cardiovascular Surgery	280 (11.1)	107 (5.3)	114 (27.5)	59 (52.2)	<0.001[a]

Values are mean ± standard deviation (median) or n (%). [a]significant difference between all risk categories. [b]significant difference between low and intermediate/high risk categories. [c]significant difference between low/intermediate and high risk categories. [d]significant difference between low and intermediate risk category.

MI, myocardial infarction; STS-PROM, Society of Thoracic Surgery Predicted Risk Of Mortality.

Clinical Outcomes

Clinical outcomes are presented in Table 2. From low to intermediate to high risk, there were stepwise increases in post-operative mortality (low 1.2% versus intermediate 2.7% versus high 6.2%), stroke (low 1.0% versus intermediate 2.4% versus high 2.7%), and renal failure (low 2.7% versus intermediate 7.2% versus high 10.6%; Figure 1). In general, the proportion of patients with any post-operative complication was higher with increasing risk (33.8% versus 47.7% versus 53.1%; $p < 0.001$).

Table 2. Clinical Outcomes

	Overall Cohort (n=2,530)	Low risk (n=2,002)	Intermediate risk (n=415)	High risk (n=113)	*p*-value
30-day mortality	42 (1.7)	24 (1.2)	11 (2.7)	7 (6.2)	<0.001[d]
Post-operative complications	935 (37.0)	677 (33.8)	198 (47.7)	60 (53.1)	<0.001[b]
Permanent stroke	34 (1.3)	21 (1.0)	10 (2.4)	3 (2.7)	0.37
Renal failure	97 (3.8)	55 (2.7)	30 (7.2)	12 (10.6)	0.001[b]
Requiring dialysis	36 (1.4)	16 (0.8)	13 (3.1)	7 (6.2)	0.03[d]
Atrial fibrillation	574 (22.6)	435 (21.7)	110 (26.5)	28 (46.7)	0.01[d]
Pneumonia	59 (2.3)	36 (1.8)	18 (4.3)	4 (3.5)	0.15
Prolonged ventilation time (>24h)	207 (8.2)	117 (5.8)	67 (16.1)	23 (20.4)	<0.001[b]
Deep sternal wound infection	7 (0.3)	6 (0.3)	1 (0.2)	0 (0.0)	0.68
Reoperation for bleeding	84 (3.3)	62 (3.1)	18 (4.3)	4 (3.5)	0.81
Reoperation other cardiac reason	38 (1.5)	33 (1.6)	5 (1.2)	0 (0.0)	0.09
Reoperation non-cardiac reasons	48 (1.9)	26 (1.3)	16 (3.9)	6 (5.3)	0.01[b]

Values are mean ± standard deviation (median) or n (%). [a] significant difference between all risk categories. [b] significant difference between low and intermediate/high risk categories. [c] significant difference between low/intermediate and high risk categories. [d] significant difference between low and high risk category.

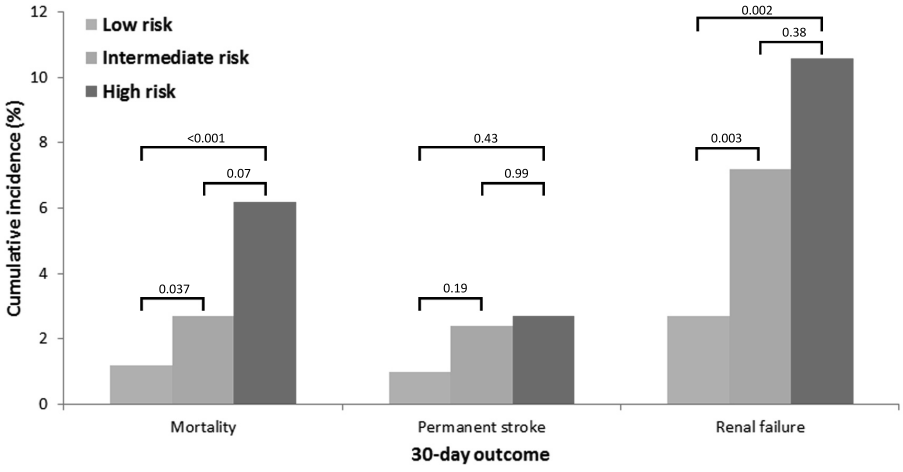

Figure 1. 30-day Clinical Outcomes

Resource Use and Costs

Resource use and costs are summarized in Table 3 and Figure 2. The hospital stay was 6.8 ± 5.1 days in the low risk category, 10.2 ± 10.2 days in the intermediate risk category, and 11.3 ± 7.4 days in the high risk category. This was reflected in the stepwise increase of hospital stay costs from low to intermediate to high risk (low $8,724 ± 8,968 versus intermediate $14,067 ± 19,276 versus high $15,962 ± 14,019; $p < 0.001$). There was no significant difference in readmission rates ($p = 0.44$). More expenses were incurred for the diagnostics of intermediate and high risk patients as compared with low risk patients (low $2,669 ± 2,439 versus intermediate $3,857 ± 4,406 versus high $4,532 ± 3,724; $p < 0.001$). The overall costs of the intervention were remarkably similar between the different risk categories ($p = 0.28$). There were higher costs of blood products in the higher risk categories (low $601 ± 1,114 versus intermediate $1,172 ± 1,982 versus high $1,305 ± 1,570; $p < 0.001$).

Interestingly the operating room costs were lower in the high risk category (low $7,516 ± 4,173 versus intermediate $7,426 ± 4,482 versus high: $6,291 ± 4,410; $p = 0.01$). There were higher costs of general supportive care according to risk category (low $3,127 ± 4,636 versus intermediate $5,692 ± 11,301 versus high $6,196 ± 7,488; $p < 0.001$). The higher rate of renal failure in the higher risk categories are reproduced in the higher costs of dialysis with increasing risk (low $34 ± 608 versus intermediate $300 ± 2,931 versus high $769 ± 2,132).

The mean total costs increased from the low to the high risk category (low $35,021 ± 22,642 versus intermediate $46,101 ± 42,460 versus high $51,145 ± 31,655; $p < 0.001$). Mean total costs for the overall cohort were $37,559 ± 27,557.

COMMENT

In a statewide prospective registry of 2,530 SAVRs, 79% of the patients was at low risk (STS-PROM 0-4%), 16% at intermediate risk (STS-PROM 4-8%), and 5% at high risk (STS-PROM>8%). Not surprisingly, clinical outcomes were worse in the higher risk categories and more resources were used. This resulted in a stepwise increase in costs from the low to the intermediate and high risk categories. Patients at high operative risk had increased 30-day mortality (low 1.2%, versus intermediate 2.7% versus high risk 6.2%), more post-operative complications (low 34% versus intermediate 48% versus high risk 53%), and longer hospitalization (low 6.8 days versus intermediate 10.2 days versus high risk 11.3 days). Mean total costs for the overall cohort were $37,559 ± 27,557. The total costs

Table 3. Resource Use and Cost Outcomes

	Overall Cohort (n=2,530)	Low risk (n=2,002)	Intermediate risk (n=415)	High risk (n=113)	*p*-value
Length of stay	7.6 ± 6.5 (6)	6.8 ± 5.1 (5)	10.2 ± 10.2 (7)	11.3 ± 7.4 (9)	<0.001[a]
Admission-surgery	0.6 ± 2.0 (0)	0.4 ± 1.6 (0)	0.9 ± 2.5 (0)	1.7 ± 3.8 (0)	<0.001[b]
Surgery-discharge	7.0 ± 6.1 (5)	6.3 ± 4.8 (5)	9.3 ± 9.9 (2)	9.6 ± 6.5 (8)	<0.001[a]
Readmission within 30 days	248 (9.8)	191 (9.5)	43 (10.4)	14 (12.4)	0.44
Total stay	9,924 ± 11,779 (7,087)	8,724 ± 8,968 (6703)	14,067 ± 19,276 (8,667)	15,962 ± 14,019 (10,991)	<0.001[b]
Emergency room	12 ± 85 (0)	10 ± 78 (0)	15 ± 85 (0)	40 ± 158 (0)	0.001[c]
ICU/CCU	8,538 ± 11,341 (5,959)	7,365 ± 8,629 (5,638)	12,689 ± 18,507 (7,701)	14,092 ± 13,742 (10,475)	<0.001[b]
Regular room	1,373 ± 2,865 (0)	1,350 ± 2,635 (0)	1,363 ± 3,474 (0)	1,830 ± 4,060 (0)	0.22
Diagnostics	2,947 ± 2,968 (2,217)	2,669 ± 2,439 (2095)	3,857 ± 4,406 (2,757)	4,532 ± 3,724 (3,812)	<0.001[b]
Radiology	358 ± 583 (196)	302 ± 443 (183)	544 ± 918 (274)	668 ± 888 (448)	<0.001[b]
Lab	2,070 ± 2,153 (1,566)	1,885 ± 1,799 (1,497)	2,695 ± 319 (1,790)	3,062 ± 2,715 (2,287)	<0.001[b]
Cardiac diagnostics	512 ± 597 (379)	477 ± 556 (353)	609 ±716 (429)	790 ± 710 (686)	<0.001[b]
Peripheral vascular lab	6 ± 46 (0)	5 ± 42 (0)	10 ± 62 0)	12 ± 51 (0)	0.07
Intervention	18,266 ± 9,750 (16,272)	18,249 ± 9,885 (16,199)	18,683 ± 9,396 (16,756)	17,041 ± 8,514 (15,026)	0.28
Anesthesia	519 ± 374 (636)	511 ± 607 (372)	537 ± 664 (369)	576 ± 959 (405)	0.47
Operating Room	7,446 ± 6,756 (4,242)	7,516 ± 4,173 (6,851)	7,426 ± 4,482 (6,647)	6,291 ± 4,410 (4,679)	0.01[d]
Recovery room	122 ± 279 (0)	129 ± 283 (0)	96 ± 275 (0)	93 ± 209 (0)	0.05
Blood products	726 ± 1,339 (223)	601 ± 1,114 (118)	1,172 ± 1,982 (552)	1,305 ± 1,570 (865)	<0.001[b]
Implants (pacers, ICD, valve)[f]	289 ± 1,830 (0)	302 ± 1,914 (0)	216 ± 1,401 (0)	312 ± 1,702 (0)	0.67
General Supplies	9,165 ± 8,021 (8047)	9,190 ± 8,231 (8,016)	9,237 ± 7,500 (8,213)	8,463 ± 5,810 (7,950)	0.63
General care	3,685 ± 6,449 (2295)	3,127 ± 4,636 (2,189)	5,692 ± 11,301 (2,791)	6,196 ± 7,488 (3,645)	<0.001[b]
Dialysis	111 ± 1,389 (0)	34 ± 608 (0)	300 ± 2,931 (0)	769 ± 2,132 (0)	<0.001[a]
Therapies (PT, OT, cardiac rehabilitation)	569 ± 1784 (257)	431 ± 1,099 (223)	1,010 ± 3,022 (390)	1,388 ± 3,849 (490)	<0.001[b]
Pharmacy	2,062 ± 3,179 (1414)	1,873 ± 2,602 (1,376)	2,821 ± 5,040 (1,559)	2,626 ± 3,192 (1,681)	<0.001[e]
Cardiac catheterization lab	116 ± 518 (0)	97 ± 472 (0)	179 ± 684 (0)	220 ± 553 (0)	0.001[e]
Respiratory therapy	820 ± 1,892 (410)	686 ± 1,381 (395)	1,362 ± 3,391 (487)	1,188 ± 1,634 (656)	<0.001
Intravenous	7 ± 136 (0)	5 ± 83 (0)	19 ± 280 (0)	4 ± 43 (0)	0.15
Other	2,737 ± 6,959 (840)	2,252 ± 8,385 (618)	3,802 ± 8,842 (1,344)	7,414 ± 15,997 (2,714)	<0.001[a]
TOTAL COSTS	37,559 ± 27,557 (31,183)	35,021 ± 22,642 (30,289)	46,101 ± 42,460 (35,327)	51,145 ± 31,655 (42,965)	<0.001[b]

Values are mean ± standard deviation (median) in U.S. dollars for year 2012. [a] significant difference between all risk categories. [b] significant difference between low and intermediate/high risk categories. [c] significant difference between low/intermediate and high risk categories. [d] significant difference between low and high risk category. [e] significant difference between low and intermediate risk category. [f] additional implants.

ICU, Intensive care unit; CCU, cardiac care unit; MI, myocardial infarction; OT, occupational therapy; PT, physical therapy; STS-PROM, Society of Thoracic Surgery Predicted Risk Of Mortality.

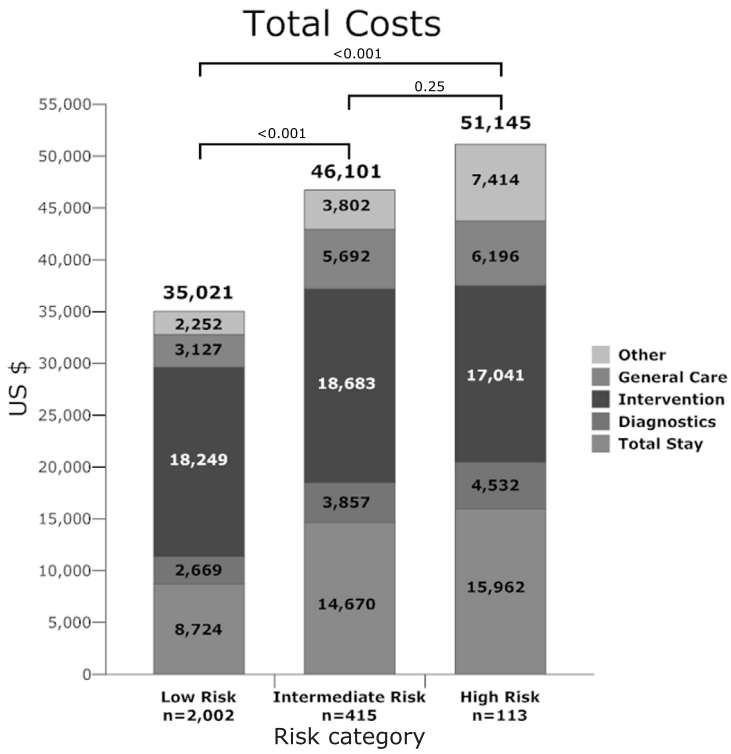

Figure 2. Total Costs of Surgical Aortic Valve Replacement

for SAVR in the different risk categories were $35,021, $46,101, and $51,145 in the low, intermediate and high risk categories, respectively.

Costs according Risk Categories

While the difference in mean total costs between the low risk category and intermediate risk category was more than $10,000, the difference between the intermediate and high risk category was less evident. Apparently, total costs are influenced in particular by the difference of having few (low risk) or more (intermediate risk) comorbidities. Subsequently, the severity or multiplicity of comorbidities (intermediate versus high risk category) have less impact on the total costs.

An explanation might be that for patients with more comorbidities, extra care and precautions are taken in any case, leading to higher costs. This might be explained by the larger difference in patients with any complication between the low and intermediate risk category (14%) as compared with the difference between the intermediate and high risk category (4%). As a supportive example, we found that general care costs, largely consisting of supplementary supporting therapies, were only slightly (approximately

$500) higher in the high risk category as compared with the intermediate category. The difference between the low and intermediate category for this cost component is considerably higher (approximately $2,500).

Limitations of risk assessment are another potential explanation for the small difference in costs between intermediate and high risk patients. Risk factors, such as frailty, are not captured in the present risk models, but are increasingly important in the elderly.[14, 15] These factors are more often present in intermediate patients, and when not captured in the risk score, some patients might be categorized as intermediate risk, while in fact they are at high operating risk. In the low risk category, this is less of an issue because these patients are younger and have less comorbidities leading to frailty and lower activity.

Frailty and other risk factors that are not included in current risk scores might also lead to selection bias in the high risk category, thereby causing the small difference in costs between intermediate and high risk patients. Patients at high risk in whom SAVR does not seem appropriate are filtered out and only those patients that are able to undergo SAVR represent a selected group. This leads to relatively moderate and similar costs in the high risk group as compared with the intermediate risk group.

Costs in the Literature

Few other studies have investigated the costs of SAVR in everyday practice. Moreover, the methodology of these studies varied significantly.[2, 16-19] One study also used charge data and found that in 1997 the mean costs of SAVR were approximately $22,000, a result that corresponds well with the $38,000 in our study when inflation is taken into account.[12, 16] Another study used the 5%-Medicare Standard Analytic Files in 2001-2008 for extracting cost data, and interpreted ICD9 codes to identify risk factors that were used as inputs for calculating the logistic EuroSCORE.[2] Subsequently patients were classified into high risk and non-high risk using a logistic EuroSCORE of 20% as the cutoff value. The costs of SAVR were $58,452 in the high risk group and $50,821 in the non-high risk group. The slightly higher outcomes than in our study could be the result of the three-month follow-up after SAVR, and the risk stratification in two EuroSCORE categories instead of the three STS-PROM categories in our study. Also, the STS and EuroSCORE models have shown a lack of correlation. It may therefore be unclear what the representative STS-PROM was for patients with >20% EuroSCORE values and in which study the risk, and consequently the costs, was higher. On the other hand, a recent study estimated costs of TAVR and SAVR procedures in intermediate risk patients, as defined by EuroSCORE, and found that the costs of SAVR were remarkably similar to our results in the intermediate risk category as defined by STS-PROM (both approximately $46,000).[18]

The current data, combined with the high burden of disease of AS, represent a large impact on the health care budget. The estimated 67,500 SAVRs and the costs of SAVR in this cohort stand for yearly health care expenditures of $2.5 billion. Currently more than 20% of the population in developed countries is over 60 years old, and a rise to approximately 28% in 2025 and 34% in 2050 is anticipated.[20] Since AS is primarily a disease of the elderly, it is expected that the burden and budget impact of AS will continue to increase.

Implications for TAVR

The results of the present study provide a benchmark for the cost of TAVR in everyday practice. The costs of high risk SAVRs in the present study are more than $20,000 lower than in the PARTNER trial.[8] Apparently, real-life index admission costs are lower than the costs in the trial ($51,145 ± 31,655 versus $74,067 ± 40,596, respectively). The costing method in the PARTNER trial was based on a combination of resource-based accounting and hospital bills. The strict selection criteria of the PARTNER trial are another potential cause of the disparity with our results. Only 12% of the screened severe AS patients were ultimately randomized in the trial resulting in limited generalizability of both clinical and economic outcomes.[5] With the costs from our study, TAVR is less likely to be an economically attractive treatment. This demonstrates the value of real-life observational studies complementary to randomized trials to establish treatment recommendations. Therefore, the final answer on the comparative cost-effectiveness of TAVR will be provided by ongoing registries with TAVR cost data from everyday practice.[21]

The SURTAVI and PARTNER II clinical trials evaluate TAVR versus SAVR in intermediate (STS-PROM 4-8) risk patients.[15] It will be interesting to see what the clinical and quality-of-life outcomes in these trials will be and how the economic outcomes compare to the $46,000 benchmark for SAVR in patients at intermediate operating risk from the current study.

Study Limitations

There are several limitations to this study. First, we did not have long-term follow-up data. A recent study showed that the 5-year follow-up costs after SAVR are considerably higher in high risk patients than in non-high risk patients.[2] However, our study is more detailed with regard to clinical characteristics and is unique by reporting costs stratified by STS-PROM risk categories that are used by the Centers for Medicare and Medicaid Services, current consensus documents, clinical guidelines and ongoing trials (ClinicalTrials.gov Identifiers: NCT01314313 and NCT01586910).[4, 15, 22, 23]

Second, there might be differences between cost items from one provider to another due to unique individual hospital coding and billing patterns. However, in a close statewide collaboration as VCSQI, disparities are minimized. Moreover, these differences will

particularly influence the categorization of costs and not the total costs on the hospital bill.

Third, there were relatively few patients in the high risk category, which may have caused the lack of statistically significant differences. This resulted in moderate power to detect differences between the intermediate and high risk categories. On the other hand, this study reported on all elective, first-time isolated SAVR in the state of Virginia during a 10 year timeframe and apparently this high risk category is relatively small.

Conclusions

Higher STS-PROM was significantly associated with higher costs, post-operative mortality, complications, and length of stay. These important data are complimentary to data from randomized trials. The SAVR cost data in the intermediate and high category provide a basis for the analysis of TAVR cost-effectiveness.

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APPENDIX

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Supplementary Table 1. Cost Categories and ICD-9 Revenue Codes

Cost Category	Revenue Codes
Emergency room	450-459
ICU/CCU	200-219
Regular room	100-179
Radiology	320-359, 400-409
Lab	300-319
Cardiac diagnostics	480, 482-489, 730-731, 739
Peripheral vascular lab	921
Anesthesia	370-379
Operating Room	360-369, 490-499
Recovery room	710-719
Blood products	380-399
Implants (pacers, ICD, valve)	275, 278
General Supplies	270-274, 276-277, 279
Pharmacy	250-259
Intravenous	260-269
Respiratory therapy	410-419
Cardiac catheterization lab	481
Therapies (PT, OT, cardiac rehabilitation)	420-449
Dialysis	800-809, 820-859, 880-889
Other	180-199, 220-249, 280-299, 470-479, 500-679, 700-709, 740-799, 901-920, 922-942, 944-999

CHAPTER 8

Costs of Transcatheter versus Surgical Aortic Valve Replacement in Intermediate-Risk Patients

Osnabrugge RL, Head SJ, Genders TS, Van Mieghem NM, De Jaegere PP, van der Boon RM, Kerkvliet JM, Kalesan B, Bogers AJ, Kappetein AP, Hunink MG.

Ann Thorac Surg. 2012;94:1954-60.

ABSTRACT

Background

Transcatheter aortic valve replacement (TAVR) offers a new treatment option for patients with aortic stenosis, but costs may play a decisive role in decision-making. Current studies are evaluating TAVR in an intermediate-risk population. We assessed the in-hospital and 1-year follow-up costs of patients undergoing TAVR and surgical aortic valve replacement (SAVR) at intermediate operative risk and identified important cost components.

Methods

We prospectively collected clinical data on 141 patients undergoing TAVR and 405 undergoing SAVR. Propensity score matching yielded 42 matched pairs at intermediate risk. Costs were assessed using a detailed resource-use approach and compared using bootstrap methods.

Results

In-hospital costs were higher in TAVR patients than in SAVR patients (€40802 vs. €33354, respectively; $p = 0.010$). The total costs at 1 year were €46217 vs. €35511, respectively ($p = 0.009$). The TAVR was less costly with regard to blood products, operating room use, and length of stay.

Conclusions

For intermediate-risk patients with severe aortic stenosis the costs at 1 year are higher for TAVR than for SAVR. The difference was mainly caused by the higher costs of the transcatheter valve and was not compensated by the lower costs for blood products and hospital stay in TAVR patients. Therefore, SAVR remains a clinically and economically attractive treatment option.

INTRODUCTION

Surgical aortic valve replacement (SAVR) is the standard treatment for patients with symptomatic aortic stenosis. However, transcatheter aortic valve replacement (TAVR) has rapidly emerged as a less invasive treatment option. A TAVR reduces mortality by 20% as compared with medical treatment in patients with severe aortic stenosis who are not eligible for surgery due to comorbidities and cardiovascular abnormalities.[1] Moreover, TAVR is equivalent to SAVR in terms of 1-year survival for patients at high risk.[2]

Therefore, considerations such as quality-of-life and costs are crucial in the decision-making process.[3] The only randomized controlled trial that reported quality-of-life in high-risk patients undergoing TAVR demonstrated a small increase in quality-adjusted life years at 1 year.[4] With equipoise in quality-of-life and survival, costs may play a pivotal role in the decision to perform TAVR or SAVR and therefore merit analysis.

Current studies evaluate TAVR in intermediate-risk populations, making the procedure more widely available. For these reasons our study assessed the in-hospital and 1-year follow-up costs of TAVR and SAVR in intermediate-risk patients with aortic stenosis using a detailed resource-use approach. A second objective was to identify important cost components.

PATIENTS AND METHODS

Study Population

Between January 2006 and November 2010 we prospectively collected data on consecutive patients with aortic stenosis who underwent self-expanding transfemoral TAVR or SAVR at the Erasmus MC, Rotterdam, the Netherlands. All patients were discussed among cardiologists, interventional cardiologists, and cardiac surgeons during heart team meetings, considering risk scores and additional factors such as frailty, porcelain aorta, and patient's preferences.[5,6] Patients underwent either TAVR (n = 141) or SAVR (n = 405). After propensity score matching 42 TAVR and 42 SAVR patients remained for the cost analysis (Table 1). One-year follow-up data was collected for all 84 propensity-matched patients. The study was approved by the Institutional Research Ethics Committee.

Resource Use and Costs

We retrospectively collected in-hospital diagnostic, procedural, and postprocedural resource use data from electronic patient records. All patients had at least 1 outpatient clinic visit prior to the procedure and several diagnostic and preprocedural tests;

Table 1. Baseline characteristics

Parameter	Before Propensity Score Matching			After Propensity Score Matching		
	TAVR (n=141)	SAVR (n=405)	*p*-value	TAVR (n=42)	SAVR (n=42)	*p*-value
Age, mean±SD (y)	81.3±6.7	70.1±9.0	<.0001	78.8±6.6	79.3±5.5	0.66
Male sex	78 (55.3)	240 (59.3)	0.41	21 (50.0)	22 (52.4)	>0.99
Logistic EuroSCORE, mean±SD	16.2±10.9	6.2±5.5	<.0001	12.9±6.8 (11.1)	12.5 ±6.4 (10.7)	0.77
Diabetes mellitus	31 (22.0)	97 (24.0)	0.64	11 (26.2)	8 (19.0)	0.61
Coronary artery disease	56 (39.7)	167 (41.2)	0.75	20 (47.6)	20 (47.6)	>0.99
LVEF			<.0001			0.68
>50%	73 (51.8)	371 (91.6)		27 (64.2)	30 (71.4)	
30-50%	55 (39.0)	29 (7.2)		14 (33.3)	10 (23.8)	
<30%	13 (9.2)	5 (1.2)		1 (2.4)	2 (4.8)	
Cerebrovascular accident	34 (24.1)	18 (4.4)	<.0001	2(4.8)	2 (4.8)	>0.99
Peripheral vascular disease	12 (8.5)	31 (7.7)	0.75	3 (7.1)	4 (9.5)	>0.99
COPD	36 (25.5)	54 (13.3)	0.001	10 (23.8)	8 (19.0)	0.77
Pulmonary hypertension	17 (12.1)	16 (3.9)	0.001	2 (4.8)	3 (7.1)	>0.99
Serum creatinine, mean±SD (µmol/l)	116.6 (94.3)	99.7 (55.7)	0.011	104.7 (92.2)	102.8 (64.6)	0.92
MI within 90 days before procedure	31 (22.0)	12 (3.0)	<.0001	0 (0.0)	4 (9.5)	0.13

COPD, chronic obstructive pulmonary disease; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; SAVR, Surgical Aortic Valve Replacement; TAVR, Transcatheter Aortic Valve Replacement.
N(%) of patients unless stated otherwise.

laboratory tests, chest X-rays, a dental consult, electrocardiography, cardiac ultrasound, coronary angiography, and lung function tests. We assumed that all patients had this standard clinical workup and that every TAVR patient underwent computed tomography. Associated costs were retrieved from the hospital's financial unit and subunits in the departments of cardiology, cardiothoracic surgery, and radiology.

The self-expanding third generation CoreValve (Medtronic, Minneapolis, MN; €17,590) was used for TAVR and SAVR was performed with the bioprosthetic Carpentier-Edwards PERIMOUNT Magna Valves (Edwards Lifesciences, Irvine, CA; €2,700). All TAVR valves were inserted through a transfemoral approach. Other materials included disposables, sutures, needles, anesthesia, sterilized gauzes, and disposables for the heart-lung machine. We retrieved these costs from the electronic ordering system and hospital pharmacy. Procedural and postprocedural blood products comprised packaged cells, fresh frozen plasma, and platelets and were priced according to The Dutch Manual for Cost-Analysis in Health Care.[7]

Interventional rooms or operating room costs were calculated as costs per minute by using a micro-costing approach. A typical surgical team that carried out SAVR consisted

of 1 cardiothoracic surgeon, 1 anesthesiologist, 1 anesthesia assistant, 1 resident, 2 nurses, and 2 technicians. Interventional teams were composed similarly, except that the team also comprised 2 interventional cardiologists, while no resident was involved. We assumed the standby time of the cardiothoracic surgeon during TAVR to be 50% of the total procedure time as he was unavailable for other surgeries. Salaries were obtained from the Manual and where necessary from collective agreements.[7]

Post-operative diagnostic tests included electrocardiography, laboratory tests, chest X-ray, cardiac ultrasound, coronary angiography, computed tomographic imaging, and lung scintigraphy. Additional procedures included chest drain placement, tracheostomy, reinterventions for pacemaker implantation, postdilatation of the transcatheter aortic valve, paravalvular leakage, sternal wound infection, and bleeding. Associated costs were retrieved using a micro-costing approach with data from financial subunits.

Data on length of stay (LOS), 1-year follow-up visits, and readmissions to the cardiology and neurology departments were collected through our electronic databases or databases from readmitting hospitals; where necessary the general practitioner was contacted. While TAVR patients were monitored in the academic hospital, SAVR patients were discharged to a general hospital to recover from surgery. After that, patients were usually discharged home. For TAVR patients, physician visits and tests were scheduled at 1 and 4 months after the initial procedure. Patients who underwent SAVR were referred to a general hospital for further follow-up. Hospital stay (€2,241, €591, and €447 per night for intensive care, academic ward stay, and general hospital ward stay, respectively) and follow-up costs were retrieved from the Manual.[7] These general average costs were based on various micro-costing studies and include physician consultations, nursing, nutrition, materials, equipment, overhead, and housing.[7]

For the individual patient costs we combined the Manual with actual costs of tests, procedures and materials as described because in the Netherlands individually specified charge data are not available. No adjustment with a cost-to-charge ratio was needed as all costs were actual costs. Furthermore, administration and overhead, maintenance of the building, and equipment were taken into account. The health care perspective was applied and consumer price indices were used to convert all costs to the year 2011.[8] The total costs at 1 year comprise the total in-hospital and follow-up costs.

Propensity Score Matching and Statistical Analysis

Comparison of the patient characteristics in the unmatched cohort was done using an unpaired *t*-test for continuous variables and using a χ^2 test or Fisher exact test for categorical variables. In the matched cohort, comparisons were performed using McNemar tests and

paired sample *t*-tests. Normality of the data was assessed using the Kolmogorov-Smirnov test and, if non-normality was proven, the Wilcoxon rank sum test was used. All tests were 2-sided with an α-level of 0.05.

The propensity score of a patient is defined as the probability to receive the experimental treatment conditional on pretreatment covariables.[9] After propensity score matching we expect TAVR and SAVR cohorts to have comparable baseline characteristics, providing a fair comparison between groups.[10] The propensity score for receiving TAVR was estimated using a multivariable probit (probability unit) model at a *p*-value less than 0.10, including gender, age, and other baseline characteristics such as logistic European system for cardiac operative risk evaluation (EuroSCORE), diabetes, coronary artery disease, left ventricular ejection fraction, creatinine level, pulmonary hypertension, peripheral vascular disease, cerebrovascular disease, and chronic obstructive pulmonary disease. Subsequently, we performed Mahalanobis 1:1 matching, where a SAVR patient is matched to a randomly chosen TAVR patient using a caliper width of 0.05.[11] The SAVR patients who were matched to a TAVR patient were no longer considered as a possible match. The resulting 42 matched pairs were used for the cost analysis.

Missing values were LOS in the intensive care unit (missing in 1 of 84 patients), length of ward stay (missing in 3), procedure time (missing in 3), and number of visits (missing in 1). The missing values were imputed by assuming they were the mean value of the non-missing values for that variable.[12]

Consistent with intention-to-treat analysis, in-hospital and follow-up costs were calculated by taking all patients (n = 84) into account, including those who died. To account for the skewed distribution of costs, we used bootstrap resampling to construct standard errors and confidence intervals of the mean costs for TAVR, SAVR, and the difference between treatments.[13]

Outliers in total costs at 1 year were defined by a Cook distance larger than 4/n, where n is the number of data points. We performed sensitivity analysis excluding outliers and their matched partners.[14] We also performed sensitivity analysis in a restricted dataset of matched pairs who did not undergo revascularization to deal with the unbalanced number of coronary revascularizations in the treatment groups. Analyses were performed by using Excel 2007 (Microsoft, Redmond, WA), SPSS for Windows (version 17.0.2; SPSS, Chicago, IL), and STATA 11.1 (Stata Corp, College Station, TX).

RESULTS

Patients and Clinical Outcomes

Baseline characteristics of the unmatched and matched cohorts are given in Table 1. The logistic EuroSCORE was 12.9 in the TAVR and 12.5 in the SAVR group, which reflects the intermediate operative risk. During SAVR, 20 patients underwent a concomitant coronary artery bypass grafting (CABG), whereas a concomitant percutaneous coronary intervention (PCI) during TAVR or as a staged procedure within the same hospital stay was performed in 3 patients (Table 2). There were no conversions from TAVR to SAVR. Procedure duration and total LOS was shorter after TAVR than after SAVR (11.3 vs. 18.8 days, respectively; Table 2). This was true for both intensive care unit stay and ward stay, taking into account the stay in our academic hospital and in the general hospital to which the patient was discharged for recovery. In our propensity matched cohort no patients were discharged to a skilled nursing facility. We found no statistically significant difference in complications, mortality at 1 year, follow-up duration, readmissions, and outpatient clinic visits (Table 2 and Table 3).

Table 2. Initial hospital stay

Parameter	TAVR (n=42)	SAVR (n=42)	*p*-value
Procedure duration, mean±SD (min)	229±79	294±76	<0.001
Concomitant PCI/CABG	3 (7.1)	20 (47.6)	<0.001
Length of post-operative stay, mean±SD (days)	11.3±8.1	18.8±13.3	<0.001
ICU	1.1±0.48	4.5±8.2	<0.001
Ward stay[a]	10.3±8.2	14.3±7.3	0.008
Ward academic hospital	10.2±8.0	7.1±4.2	0.004
Ward general hospital	0.14±0.93	7.2±6.6	<0.001
In-hospital complications[b]	22 (52.4)	14 (33.3)	0.08
Major stroke	4 (9.5)	1 (2.4)	0.38
MI	0	1 (2.4)	>0.99
Major bleeding	4 (9.5)	5 (11.9)	>0.99
Major vascular	4 (9.5)	0 (0.0)	0.13
Reintervention	2 (4.8)	5 (11.9)	0.45
Infection	7 (16.7)	5 (11.9)	0.77
PPI	6 (14.3)	1 (2.4)	0.13
Pneumothorax	0 (0.0)	1 (2.4)	>0.99
In-hospital mortality[b]	2 (4.8)	3 (7.1)	>0.99

Abbreviations as previous; CABG, coronary artery bypass graft; ICU, Intensive Care Unit; PCI, percutaneous coronary intervention; PPI, permanent pacemaker implantation;
N(%) of patients unless stated otherwise.
[a]All patients were operated in the academic center. Patients who underwent TAVR were usually discharged home, whereas patients who underwent SAVR were usually discharged to a general hospital for recovery.
[b]In-hospital mortality is defined as death <30 days after procedure or death during initial hospital stay.

Table 3. Follow-up

Parameter	TAVR (n=42)	SAVR (n=42)	*p*-value
1 year follow-up death	7 (16.7)	5 (11.9)	0.73
Mean follow-up, mean±SD (days)	332.1±88	339.8±88	0.51
Outpatient clinic visits, n of patients (%)	33 (78.6)	35 (83.3)	0.75
Number of outpatient clinic visits per patient, n ±SD	1.8±1.8	2.0±1.6	0.24
Hospital readmission during follow-up[a], n of patients	8 (19.0)	10 (23.8)	0.80
Hospital readmissiona, days ±SD	5.3±19.0	2.4±7.7	0.86

Abbreviations as previous.
[a]Reasons for readmission included dyspnea, chest pain, endocarditis of the prosthesis, cardiac arrhythmias, additional dilatation of the valve, reoperation, transient ischemic attack and heart failure.

In-Hospital Costs

The in-hospital costs were higher with TAVR than SAVR (€40,802 vs. €33,354, respectively; Table 4). The largest difference was found in the procedure costs (€28,785 vs. €13,096, respectively) and in-hospital stay (€8,481 vs. €17,409, respectively). Procedural cost components that were significantly different between the treatment groups were operating room use, materials, and blood products (Table 4).

Table 4. In-Hospital Costs

Parameter (mean±SE)	TAVR (n=42)	SAVR (n=42)	*p*-value
Pre-operative costs	2024±0	1538±0	
Procedure costs	28785±1014	13096±315	<0.001
Operating room use	1124±60	453±18	<0.001
Personnel	2303±117	2431±90	0.41
Materials	22055±869	5162±0	<0.001
Blood products	176±41	1869±223	<0.001
Overhead and housing	3127±48	3181±38	0.40
Total stay	8545±776	17409±3116	<0.001
ICU stay	2458±168	9991±2820	0.008
Ward stay[a]	6087± 733	7418±544	0.087
academic hospital	6023±715	4208±370	0.016
general hospital	64±64	3210±446	<0.001
Post-operative tests	545±50	674±108	0.31
Post-operative blood products	136±43	63±27	0.17
Additional procedures	768±273	573±209	0.56
Total in-hospital costs	40802±1399	33354±3357	0.010

Euros for year 2011.
Abbreviations as previous.
[a]All procedures were performed in the academic center. TAVR patients were usually discharged home, whereas SAVR patients were usually discharged to a general hospital for recovery. The subdivision of ward stay reflects this difference.

Follow-Up Costs

The costs incurred during follow-up were nonsignificantly higher in the TAVR group than in the SAVR group (Δ costs = €3,258; Table 5). In addition, components of the follow-up costs were not significantly different. The total costs at 1 year were higher for TAVR than for SAVR (€46,217 vs. €35,511, respectively; $p = 0.009$; Fig 1).

Table 5. One-Year Follow-Up Costs

Parameter (mean±SE)	TAVR (n=42)	SAVR (n=42)	*p*-value
Visit costs	182±28	135±16	0.10
Visit diagnostic tests	582±86	587±69	0.97
Readmission hospital stay	3336±1882	1086±528	0.25
Readmission procedures	1168±589	245±172	0.13
Readmission diagnostic tests	146±59	104±41	0.58
Total one-year follow-up	5414±2224	2157±627	0.17

Euros for year 2011.
Abbreviations as previous.

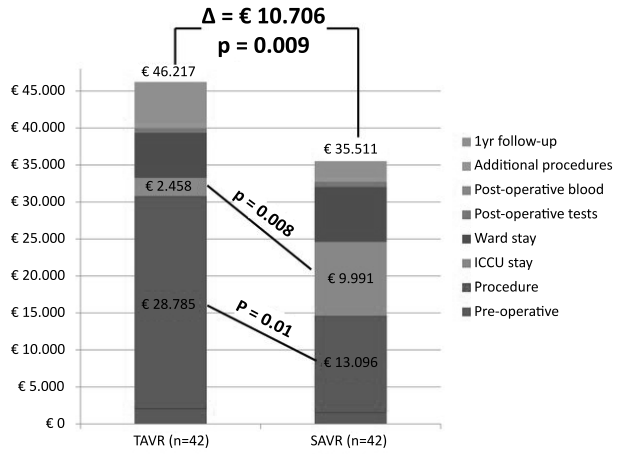

Figure 1. Total Costs at 1 Year
Euros for year 2011.
Blocks containing numbers represent cost components which differ significantly between treatment groups. ICCU, intensive cardiac care unit; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Sensitivity Analyses

We identified 3 outliers due to prolonged postprocedural or readmission hospital stay. In a sensitivity analysis of the remaining 39 pairs we found similar results as in the original analysis for in-hospital costs (€39,945 vs. €29,251; $p < 0.001$), follow-up costs (€3,426 vs. €2,286; $p = 0.37$), and total costs at 1 year (€43,370 vs. €31,537; $p < 0.001$) for TAVR and SAVR, respectively.

In the sensitivity analysis of 22 matched pairs who did not undergo revascularization we found in-hospital costs of €40,154 (standard error of the mean [SE] = 1,504) for TAVR and €26,776 (SE = 1,087) for SAVR (Δ costs = €13,378; $p < 0.001$). The total costs at 1 year were, respectively, €48,102 (SE = 4,800) and €29,349 (SE = 1,608) ($p < 0.001$).

COMMENT

The results of our study suggest that TAVR is significantly more expensive than SAVR for intermediate-risk patients with aortic stenosis. This conclusion refers to both the in-hospital costs and the total costs at 1 year. The difference is mainly explained by the costs of materials, which was roughly 4 times higher in TAVR than SAVR. The fact that the patients in the TAVR group were less costly with regard to blood products and LOS did not outweigh the difference in costs of materials (Fig 1). Furthermore, close monitoring of TAVR patients may explain the trend toward higher follow-up costs.

The costs of the procedure were higher for TAVR than for SAVR (Table 4), while procedure times with TAVR were shorter (Table 2). This can be explained by the more expensive equipment in intervention rooms than in the operating room (€1.54 vs. €4.91 per minute for TAVR and SAVR). However, room use is only a fraction of the overall procedural costs (Table 4).

We observed more revascularizations in patients undergoing SAVR because guidelines recommend concomitant CABG for patients with moderate to severe coronary artery disease;[15] no such recommendations exist for TAVR. In the sensitivity analysis of matched pairs who did not undergo revascularization we found that the difference in costs between TAVR and SAVR was larger than in the original analysis. A concomitant procedure such as CABG is likely to make SAVR more expensive as the procedure and hospital stay may take longer and the complication rate is higher.[16] However, PCI in addition to TAVR has shown to be of less influence on procedural and midterm outcomes.[17] From an economic perspective, an additional advantage for SAVR is to be expected if PCI and TAVR are performed as staged procedures.

The transcatheter valve is currently priced at €17,590, whereas the surgical aortic bioprosthesis costs only €2,700. With more valves being developed, market forces are likely to decrease the price of transcatheter valves, similar to the trend previously seen in coronary stents.[18] Using the mean difference in costs at 1 year and the price of the transcatheter valve, we calculated that the valve would have to be priced at €6,884 to be a cost neutral alternative for SAVR.

One other study reported the costs of TAVR, showing quite different estimates compared with our results.[19] The discordance with our study might be caused by different cost calculation methods, which were briefly described and partly based on a costing study of percutaneous pulmonary valves. In studies that used the in-hospital costs for SAVR, the estimates were also quite different from our results.[16,20] However, comparison is difficult as none of these studies primarily focused on costs and therefore the methodology for assessing costs varied and was not very detailed.

We have found no published report that compared costs in TAVR versus SAVR in intermediate-risk patients. In the high-risk patients of the PARTNER (Placement of Aortic Transcatheter Valve) trial the total costs at 1-year follow-up were higher than the costs in our study.[4] Moreover, there was no significant difference in costs between TAVR and SAVR. In comparison with our results, the nonprocedural costs were higher, whereas the LOS and other resource use were similar. Differences might therefore be attributed to higher costs of hospital stay in the United States.[21]

Using our results we can make some crude statements on the cost effectiveness of TAVR versus SAVR. The PARTNER trial showed a quality-of-life gain of 0.068 at 1 year for TAVR as compared with SAVR [4]. Combining our cost results with this quality-of-life gain yields an ICER (incremental cost-effectiveness ratio) of around €150,000 per quality-adjusted life year saved, which in general is considered higher than the threshold willingness-to-pay. Although ICERs should be calculated using life-time costs, 1-year follow-up costs in our study were similar for the 2 treatments and show that periprocedural costs will be the driver of cost effectiveness of TAVR. However, more elaborate analyses are needed to confirm these results.

Limitations

Cost data were not based on a randomized trial but were retrospectively collected from a relatively small single-center observational study. However, economic data from well-performed observational studies are equally valuable to policy makers as such data reflect the real-life economic consequences of new treatments.[22] Moreover, industry sponsored economic evaluations alongside trials are more likely to report favorable results,[23] increasing the value of independent economic observational studies.

To overcome the limitation that our study was not randomized, we used propensity score matching. This technique corrects for measured confounders but there may have been unmeasured confounding in our study. However, we used a very conservative caliper in the matching process while other studies have used wider margins.[24] The statistically

similar clinical outcomes in the matched cohort allow for a valid cost comparison between the groups.

Because propensity score matching does not take into account procedural variables, it was possible that we found an imbalance in the concomitant revascularization rate. A regression model could adjust for this imbalance but makes assumptions on the distribution of the outcome variable and would require more revascularizations in the TAVR group. Due to the skewed nature of cost variables and the small sample size, the distribution free bootstrap method is preferred.[13]

Since 2005 our center has performed roughly 250 TAVRs, whereas there is a multitude of experience with SAVR. This may result in longer procedures, more personnel being present, and longer hospital stay. As experience with TAVR in intermediate-risk patients develops, and with the refinement of techniques and protocols, it is likely that costs, LOS, and complication rates will decrease.

The logistic EuroSCORE was used as a matching variable and indicator of operative risk. The score fails to include factors such as porcelain aorta, frailty, chest deformities, and malnutrition. Therefore we might have underestimated the operative risk of TAVR patients, leading to higher costs in this group. It is unlikely that this affected the main conclusion of our study as the cost of the transcatheter valve is the main cause of the difference in costs between the 2 groups.

In the current study the costs were specific for Dutch centers. However, our results may be translated to other countries using regression techniques.[25] These models can adjust for differences in the cost of medical treatments due to demography, epidemiologic factors, and differences in medical practice, resource use, and funding of health care.

Conclusions

For intermediate-risk patients with severe aortic stenosis the costs at 1 year are higher for TAVR than for SAVR. The difference was mainly caused by the higher costs of the transcatheter valve and was not compensated by the lower costs for blood products and hospital stay in TAVR patients. Therefore, SAVR remains a clinically and economically attractive treatment option.

ACKNOWLEDGEMENTS

The authors acknowledge the contributions of J.C. van der Baan, D.J.C. de Haas, J.G. Duys-Huizinga, K. Ijntema, and A.M. Maugenest for their assistance in collecting cost data.

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CHAPTER 9

Transcatheter Aortic Valve Implantation (TAVI): Risky and Costly, or Challenging and Promising?

Osnabrugge RL, Head SJ, Kappetein AP.

BMJ. Letter to the editor. August 15, 2012.

TO THE EDITOR:

With great interest we read the commentary on transcatheter aortic valve implantion (TAVI) by Van Brabandt and colleagues in a recent issue of the *Journal*.[1] The authors raised concerns regarding the continued access population and baseline imbalances in the PARTNER trial and the early termination of the STACCATO trial. They also commented on the approval process and concluded that the widespread use of TAVI is not supported by sufficient evidence. We acknowledge their thorough analysis, but some of their arguments need to be put into perspective.

Van Brabandt et al. suggested adjustment for imbalances at baseline, but such analyses are hampered by covariate selection and rarely influence the overall conclusion of a clinical trial.[2] Also, the randomisation process in the PARTNER trial was well done and with more extensively calcified aorta in the TAVI group (19.0%) than in the standard treatment group (11.2%), it is not apparent that the baseline imbalances favoured TAVI. The steering committee consisted of both surgeons and cardiologists to balance potential differences in opinions and interests. Accusations that conflict of interests influenced the results are easily made but should be substantiated.

It is conspicuous that the authors, despite their extensive efforts, could not retrieve more details of the continued access population. However, the results of this relatively small patient group are unlikely to change the overall conclusion of PARTNER B with its 25% mortality reduction at two-year compared to standard treatment.[3] Although an elaborate discussion with a large panel of experts is publicly available,[4] we agree that publishing study design, patient characteristics and detailed results of the continued access population would relieve concerns.

Van Brabandt et al. insinuated that one of the PARTNER investigators, commenting on the STACCATO trial, was more concerned with the field than with his patients. With this bold statement, the authors ignored the serious methodological and ethical issues of the STACCATO trial. The only inclusion criterion (an age>70 years) led to TAVIs in the lowest risk category ever reported (STS score of 3.1) and flawed power calculations put patients at risk while knowing that the trial would not be able to provide a reliable answer.[5] Due to these issues, the STACCATO results contribute virtually nothing to the scientific appraisal of TAVI.

We agree with the authors that the uptake of TAVI has been rapid and that the European regulations for the introduction of high-risk medical devices seem outdated. Taking into account the mentioned issues, we believe that the evidence is hopeful for TAVI. This new

technique should be evaluated with scientific rigor and transparency and in light of the continuous refinement of techniques. A major challenge is how to reduce the number of complications. The PARTNER trial however showed the results of the first experience with the first generation of TAVI. With newer techniques, like embolic protection devices, increased experience, and newer generation devices, the future looks promising.

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CHAPTER 10

Non-Cardiac Surgery in Patients with Severe Aortic Stenosis: Time to revise the Guidelines?

Osnabrugge RL, Kappetein AP, Serruys PW.

Eur Heart J. 2014; 35:2346-48.

Many patients undergoing major non-cardiac surgery have a high risk of perioperative cardiovascular complications. Several studies have identified variables that are associated with this increased perioperative cardiovascular risk,[1-3] including arrhythmias, heart failure, recent myocardial infarction, and ischemic heart disease. Aortic stenosis (AS) is not always included in cardiac risk predictions models, because it is regularly underdiagnosed and therefore also underrepresented in databases and the resulting risk assessment tools. Nevertheless, severe AS is the most prevalent valvular heart disease in the elderly,[4] of which many regularly require non-cardiac surgery.

Patients with AS have an obstruction in the outflow tract that gradually results in left ventricular myocardium hypertrophy. Initially, the cardiac output and left ventricular end-diastolic volumes are preserved, permitting patients to stay asymptomatic. Eventually however, the concentric left ventricular hypertrophy and reduced compliance of the myocardium leads to diastolic dysfunction. At that point, patients develop symptoms of dyspnea or chest pain due to the increased diastolic pressure of the left ventricle. In addition, the AS causes systemic hypotension and reduction of coronary flow reserve. When patients in this condition are exposed to the hemodynamic stress as in major surgical procedures, they are at higher risk of decompensated heart failure.

Therefore, the European Society of Cardiology (ESC), European Association of Cardio-Thoracic Surgery (EACTS) and American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines dedicate special sections describing decision-making in non-cardiac surgery for patients with severe AS.[5-7] These guidelines recommend to postpone or cancel non-cardiac surgery if severe AS is symptomatic and surgical or transcatheter aortic valve replacement prior to non-cardiac surgery should be considered. For asymptomatic patients, the AHA guideline suggests postponing non-cardiac surgery if the valve has not been evaluated within 1 year.[5] The ESC/EACTS guideline recommends to proceed with non-cardiac surgery in asymptomatic patients that are at low or moderate surgical risk for the non-cardiac surgery, whereas in high risk patients, the patients' risk for surgical aortic valve replacement is decisive (Figure 1A).[7] These recommendations are largely based on small and old observational studies.[1, 8-11]

In this edition of The Journal, Tashiro et al. present a large contemporary study of patients with severe AS undergoing moderate to high risk non-cardiac surgery.[12] By linking more than 500,000 echocardiograms with their surgical database, the authors were able to identify 256 patients with severe AS. These patients were matched to patients without AS based on age-, gender and year of surgery. There was no significant difference in 30 day mortality (5.9% vs. 3.1%, $p = 0.13$). The rate of MACE (death, stroke, myocardial infarction, ventricular tachycardia/fibrillation, and heart failure) was higher in the severe

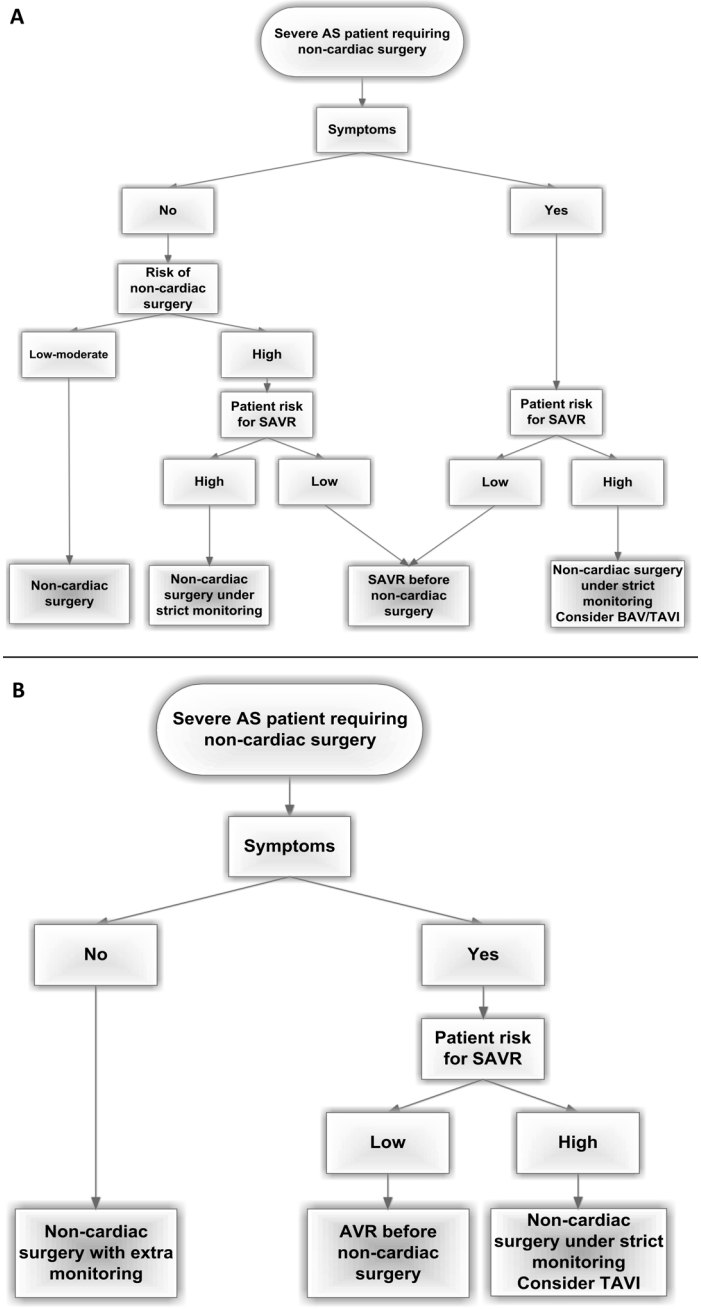

Figure 1. Decision-Making in Severe Aortic Stenosis for Patients who require Non-Cardiac Surgery
Panel A: based on the current ESC/EACTS guidelines.[7]
Panel B: suggested decision-making flowchart when the study by Takashiro is incorporated.[12]
AS, aortic stenosis; BAV, balloon aortic valvuloplasty; SAVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation

AS group (18.8% vs. 10.5%, $p = 0.01$), mainly due to higher rates of heart failure. In addition, emergency surgery was shown to be the strongest predictor of 30 day mortality.

This important study has several implications for perioperative management of patients with severe AS and may even lead to revision of aforementioned guidelines. The perioperative mortality rate was lower than previously reported. Therefore the authors speculate that the threshold to proceed with the non-cardiac surgical procedure without treating a severe AS could be lowered.[12] There are several potential reasons for the relatively low rate of mortality in the current study, including improvements in surgical and anesthesia techniques compared to earlier studies. However, outcomes in the symptomatic group (n = 106) were markedly worse than in the asymptomatic group (n = 150). In asymptomatic patients and their matched controls, mortality and MACE rates were practically equal (around 3% and 10-12% in both patients with and without AS). On the other hand, in the patients with symptoms, MACE at 30 days was significantly higher compared to their controls (28.3% vs. 8.5%, $p < 0.001$), although the difference in mortality (9.4% vs. 3.8%) did not reach statistical significance ($p = 0.097$). This suggests that the excellent outcomes of patients with severe AS might be restricted to asymptomatic patients. This strengthens the guidelines noting that the non-cardiac surgical management of patients with severe AS mainly depends on the presence of symptoms.[5, 7] This is further supported by a recent study that found that the presence of symptoms was a predictor of worse outcomes.[13] Only when the prolonged AS results in considerable physiologic changes and apparent symptoms of dyspnea or chest pain, clinicians should consider treatment of this condition prior to non-cardiac surgery. In those patients with symptomatic severe AS, TAVI could serve as an alternative to surgical aortic valve replacement and should be preferred over balloon aortic valvuloplasty.[14] Careful intraoperative monitoring and an intensive team effort with the anesthesiologist is recommended in these severe AS patients undergoing non-cardiac surgery.

In a field where randomized trials are unlikely and observational evidence is scarce, the current study shows that moderate or high-risk non-cardiac surgery in patients with severe, asymptomatic AS can be performed safely. Until now, the existing evidence on non-cardiac surgery in patients with severe asymptomatic AS was largely based on one study describing low to moderate non-cardiac surgical procedures.[15] With the results of the study by Tashiro et al. non-cardiac surgery of any risk should rarely be postponed because of the presence of asymptomatic severe AS (Figure 1B). With these new important insights, it might be time to revise the guidelines.

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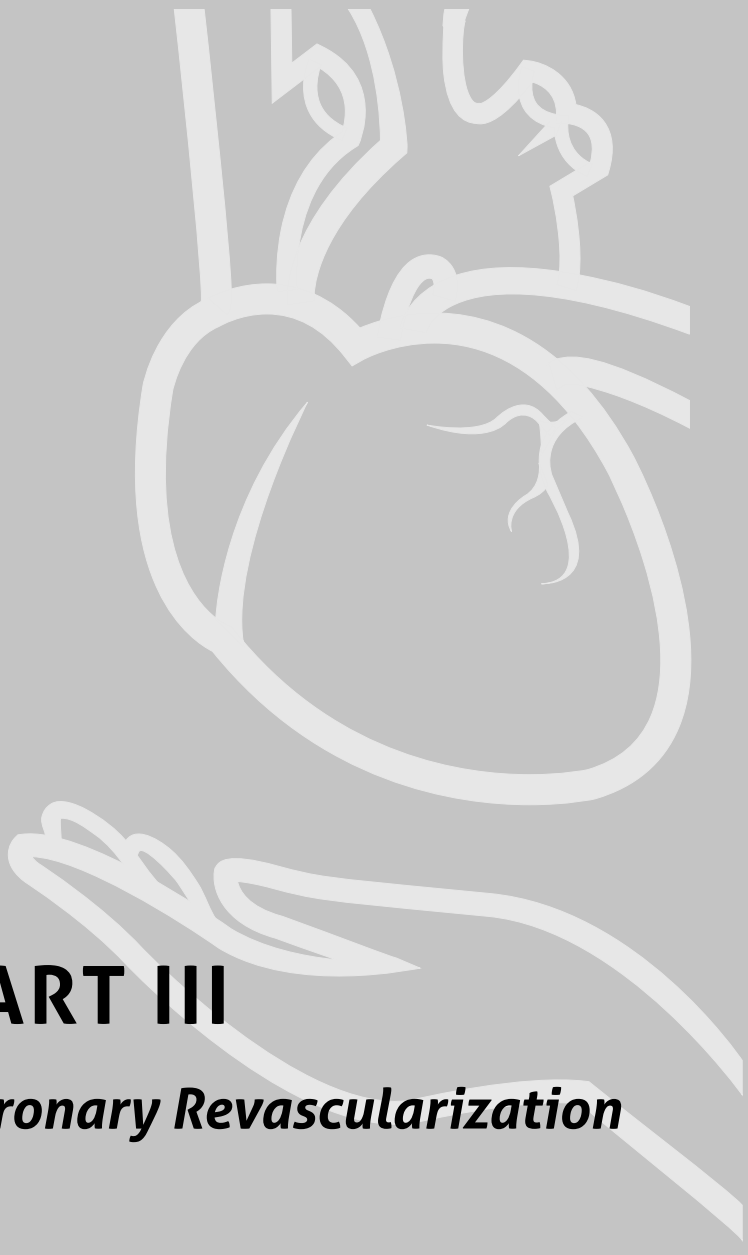

PART III

Coronary Revascularization

CHAPTER 11

Cost-Effectiveness of Percutaneous Coronary Intervention with Drug-Eluting Stents vs. Bypass Surgery for Patients with 3-Vessel or Left Main Coronary Artery Disease: Final Results from the SYNTAX Trial

Osnabrugge RL*, Cohen DJ*, Magnuson EA, Wang K, Li H, Chinnakondepalli K, Pinto D, Abdallah MS, Villain KA, Morice MC, Dawkins KD, Kappetein AP, Mohr FW, Serruys PW.

**shared first authorship*

Circulation. 2014;130:1146-57.

ABSTRACT

Background

The SYNTAX trial demonstrated that in patients with 3-vessel or left-main CAD, CABG was associated with a lower rate of cardiovascular death, MI, stroke, or repeat revascularization compared with DES-PCI. The long-term cost-effectiveness of these strategies is unknown.

Methods and Results

Between 2005 and 2007, 1800 patients with left-main or 3-vessel CAD were randomized to CABG (n = 897) or DES-PCI (n = 903). Costs were assessed from a US perspective, and health state utilities were evaluated with the EuroQOL questionnaire. A patient-level micro-simulation model based on the 5-year in-trial data was used to extrapolate costs, life expectancy, and quality-adjusted life expectancy over a lifetime horizon.

Although initial procedural costs were $3415/patient lower with CABG, total hospitalization costs were $10,036/patient higher. Over the next 5 years, follow-up costs were higher with DES-PCI, owing to more frequent hospitalizations, revascularization procedures, and higher medication costs. Over a lifetime horizon, CABG remained more costly than DES-PCI but the incremental cost-effectiveness ratio was favorable ($16,537/QALY gained) and remained <$20,000/QALY in most bootstrap replicates. Results were consistent across a wide range of assumptions regarding the long-term effect of CABG vs. DES-PCI on events and costs. In patients with left-main disease or a SYNTAX Score ≤22, however, DES-PCI was economically dominant compared with CABG although these findings were less certain.

Conclusions

For most patients with 3-vessel or left-main CAD, CABG is a clinically and economically attractive revascularization strategy compared with DES-PCI. However, among patients with less complex disease, DES-PCI may be preferred on both clinical and economic grounds.

INTRODUCTION

Approximately 6% of all American adults suffer from coronary artery disease (CAD) with estimated total annual costs in excess of $200 billion.[1] Coronary revascularization procedures including percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) account for nearly $12 billion/year in direct costs alone. Over the past 2 decades, numerous clinical trials have compared the clinical outcomes of PCI vs. CABG for patients with multivessel CAD. In general, these studies have demonstrated similar short- and long-term mortality with either procedure (with the exception of diabetic patients) but substantial advantages of CABG in terms of angina relief and the need for subsequent revascularization procedures.[2-8] Economic evaluations performed in both the balloon angioplasty and bare metal stent eras, have consistently demonstrated early cost savings with PCI but similar long-term costs for the 2 strategies.[7, 9, 10]

The most recent study to compare PCI with CABG in a broad population was the SYNTAX trial.[11] In contrast to previous studies, SYNTAX included patients with more complex CAD (3-vessel and left main disease), had few exclusion criteria, and used drug-eluting stents (DES) for all PCI procedures. At 5-year follow-up, SYNTAX demonstrated that CABG was associated with a lower rate of the composite of cardiovascular death, MI, stroke, or repeat revascularization compared with DES-PCI—driven mainly by reductions in non-fatal MI and repeat revascularization.[12] However, DES-PCI was associated with a lower rate of stroke in the overall population and similar overall clinical outcomes in certain patient subsets.[12, 13] Given the current economic challenges facing virtually all healthcare systems, understanding both the long-term clinical benefits and cost-effectiveness of these alternative revascularization strategies is critical for both clinical guideline development and health care policy. We therefore performed a prospective health economic evaluation alongside the SYNTAX trial. Although the SYNTAX trial included only 5-year follow-up, we used disease-simulation techniques to extrapolate the 5-year trial results to a lifetime horizon.

METHODS

The design and methods of the SYNTAX trial have been described previously.[11, 12, 14] Between March 2005 and April 2007, 1800 patients with 3-vessel or left main CAD without recent MI who were considered equally suitable for PCI with DES and CABG by both a cardiac surgeon and an interventional cardiologist were randomized to either procedure. CABG was performed using standard techniques, and PCI procedures utilized paclitaxel-eluting stents (TAXUS Express, Boston Scientific, Natick, MA, USA). The institutional review board at each participating site approved the protocol and all patients provided written

informed consent. The trial complies with the Declaration of Helsinki and is registered at the National Institutes of Health website (http://www.clinicaltrials.gov; identifier NCT00114972).

Estimation of Medical Care Costs

Costs for the initial hospitalization and the 5-year follow-up period were assessed by a combination of resource-based and event-based methods as described below. These methods were virtually identical to those used for a recent health economic assessment of DES-PCI vs. CABG among diabetic patients.[15] To maintain consistency with that previous report, all costs were assessed from the perspective of the U.S. health care system and are reported in 2010 U.S. dollars.

Procedural Costs

Detailed resource use was recorded for each initial and any subsequent revascularization procedures, and the cost for each item was estimated on the basis of its mean hospital acquisition cost at 3 surveyed U.S. hospitals. Each DES was assigned a cost of $1500. Costs of antithrombotic therapy were based on the current wholesale acquisition cost obtained from Micromedex Red Book.[16] Costs for additional disposable equipment, overhead and depreciation of the cardiac catheterization laboratory and operating room, and non-physician personnel were estimated using data from the micro-cost accounting systems of Saint Luke's Mid America Heart Institute and adjusted for observed procedure duration. For the purposes of this report, initial and planned staged PCI procedures were combined for the calculation of index resource utilization and cost.

Post-Procedure Hospitalization Costs

Post procedure costs for each initial hospitalization were estimated using regression models based on SYNTAX-eligible patients who underwent either PCI (n = 113,921) or CABG (n = 43,866) and whose data were included in the 2010 Medicare Provider and Review (MEDPAR) database. Hospital charges were converted into costs using hospital- and cost center-specific cost-to-charge ratios.[17, 18] Linear regression models were then developed, using total hospitalization costs as the outcome and sociodemographic factors, comorbidities, and in-hospital complications (identified on the basis of ICD-9 codes) as predictors (Supplementary Table 1). Because of substantial variability in length of stay for revascularization procedures across the enrolling countries, length of stay was not included as a predictor in these models. The final models for PCI and CABG were then used to predict nonprocedural costs for each initial hospitalization as well as any subsequent hospitalizations that involved coronary revascularization. To avoid double-counting procedural costs, the intercept for each model was adjusted to remove the costs directly related to the revascularization procedures.

For follow-up cardiovascular hospitalizations that did not involve a revascularization procedure, Medicare Severity-Diagnosis Related Groups (MS-DRGs) were assigned based on the primary indication for hospitalization and procedures performed during that admission. Costs were then assigned based on mean 2010 Medicare reimbursement rates for the MS-DRG obtained from the Medicare Part A data files.[19]

Physician Costs

Physician fees for PCI and CABG procedures (including those for the primary surgeon, surgical assistant, and anesthesiologist) were based on the 2010 national Medicare fee schedule. Non procedure-related physician fees for revascularization-related hospitalizations were estimated for U.S. patients on the basis of post procedure ICU and non-ICU length of stay and Medicare payment rates. For non-U.S. patients, postprocedure length of stay after CABG and PCI was estimated from regression models developed using 2010 MedPAR data and the same covariates as used in the cost models (Supplementary Table 2), along with PCI and CABG-specific ratios of ICU vs. total post procedure length of stay estimated from the trial data for U.S. patients. Physician costs for all other hospitalizations were estimated as a percentage of hospital costs according to the Medicare Severity-Diagnosis Related Group.[20, 21]

Outpatient Costs

Costs for outpatient visits, tests and procedures, and inpatient rehabilitation and skilled nursing facility days were estimated using 2010 Medicare reimbursement rates. Outpatient medication use was assessed at each follow-up visit, and costs were assigned using the most current average wholesale prices from Micromedex Red Book.[16]

Quality of Life

Quality of life was assessed directly from patients at baseline and at 1, 6, 12, 36, and 60 months using the EuroQOL (EQ-5D) health status instrument and converted to utility weights (range 0-1) using an algorithm developed from the U.S. population.[22]

Statistical Analysis

To account for the slightly higher withdrawal rate among patients assigned to CABG, a modified intention-to-treat (mITT) population was used as the primary population for economic analysis. This population was defined as all randomized patients who underwent ≥1 initial revascularization procedure (n = 1766), with patients categorized according to their assigned treatment. Since virtually all of the patients who did not undergo revascularization withdrew from the trial within the first 6 months of follow-up, the MITT approach is preferred because it includes initial revascularization costs for all patients while yielding survival estimates that are virtually identical to those for an ITT analysis using censored

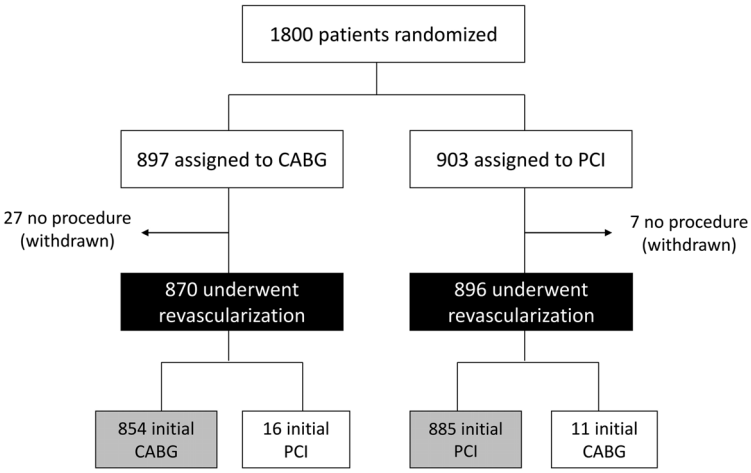

Figure 1.
CONSORT diagram. Black boxes represent the modified intention-to-treat (mITT) population that was the primary analytic population for the economic study. The grey boxes represent the per protocol (PP) population. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

data. A secondary analysis used the per protocol (PP) population and included only those patients who underwent the assigned revascularization procedure (n = 1739).

Categorical data are reported as frequencies, and continuous data are reported as mean ± standard deviation. Discrete variables were compared using Fisher exact tests. Normally distributed continuous variables were compared using Student *t*-tests, and non-normally distributed data were compared using the Wilcoxon rank-sum test. Treatment effects from Poisson regression models were used for the comparison of hospitalization rates. Kaplan-Meier estimates and log-rank tests were used for the comparison of 5-year clinical events. Cost data are reported as both mean and median values and were compared using *t*-tests.[23] Confidence intervals for the differences in costs between treatment groups were obtained via bootstrapping (1000 replicates).[24]

Quality-adjusted life expectancy was calculated for each patient as the time-weighted average of his/her utility values. The mid-point between assessments was used as the transition between health states, starting at the 30-day visit. Missing utility values were estimated using multiple imputation, taking into account baseline patient characteristics, clinical events including hospitalizations, and previous utility values.

In-Trial Analysis of Costs, Life years, and Quality-Adjusted Life Years

Since not all patients had complete 5-year follow-up data, methods for the analysis of censored data were used to obtain estimates of cumulative costs and quality-adjusted

life-years (QALY) at each follow-up timepoint.[25] We used Kaplan Meier methods to estimate survival at each follow-up timepoint, and life expectancy differences were estimated as the area between the 2 survival curves. For costs, an inverse probability-weighted estimator was applied, whereby the time axis was divided into 3-month intervals, and costs for each interval were estimated as the observed costs during the interval for patients with complete data divided by the probability of not being censored within the interval. Similar methods were applied to estimate QALYs. The bootstrap method was used to calculate the confidence limits for the mean cumulative cost, life-year, and QALY estimates for each treatment group, as well as the difference between groups.[24]

Cost-Effectiveness

The cost-effectiveness of CABG vs. PCI was assessed over a life-time horizon using QALYs as the measure of health benefit for the primary analysis, and life-years for secondary analyses.[26] Costs, life-years, and QALYs were discounted at 3% per year for all cost-effectiveness calculations.[27] The lifetime analyses were based on a combination of (1) observed in-trial cost and quality of life data and (2) projections of post-trial costs, life expectancy and quality-adjusted life expectancy obtained from a Markov disease-simulation model. In this model, each surviving patient was assumed to face a monthly risk of death, with estimates of this risk based on the age-, sex- and race specific risk of death obtained from U.S. life tables, which were calibrated to match the observed 5-year mortality for the SYNTAX PCI population.[15, 28]

For the CABG group an additional multiplicative factor was applied to project the benefit of CABG vs. PCI on mortality. This multiplier was based on the hazard ratio (HR) derived from an analysis of all-cause mortality from the SYNTAX patients. In a sensitivity analysis, the separate impact of non-fatal myocardial infarction (MI) and stroke on long-term mortality was taken into account. For these secondary analyses, HRs were obtained from a Cox proportional hazards regression model fit to the trial data, in which non-fatal MI and stroke were each modeled as time-dependent covariates, and baseline characteristics (age, sex and diabetes) and treatment group were included as fixed covariates. Patient-level costs and utility weights for each projected year of life beyond the trial observation period were derived from regression models developed from the in-trial data (Supplementary Tables 3 and 4).

Three sets of analyses were performed based on alternative assumptions regarding the duration of the prognostic benefit of CABG relative to PCI. The base case analysis assumed that the benefit of CABG tapered in a linear fashion from year 5 to 10 and that there were no prognostic differences between PCI and CABG beyond year 10 (i.e. HR=1

after year 10). In sensitivity analyses, we assumed that (1) prognostic benefits of CABG would remain constant from year 5 to year 10, with no benefit of CABG after 10 years; or 2) that there would be no further prognostic benefit of CABG beyond the 5-year trial observation period (i.e. HR=1 after year 5).

Bootstrap methodology (1000 replicates) was used to estimate uncertainty in the joint distribution of lifetime cost, life-years, and QALYs for each treatment group. To maintain consistency of the within-trial and post-trial CABG effect within each bootstrap sample, the HRs for the effect of CABG vs. PCI on mortality were re-estimated for each bootstrap replicate. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC.).

Table 1. Baseline Characteristics (mITT population)

	CABG (n=870)	PCI (n=896)	*p*-value
Sociodemographic characteristics			
Age, y	64.9 ± 9.8	65.3 ± 9.6	0.40
Male, %	79.4	76.6	0.15
Body mass index, kg/m^2	27.9 ± 4.4	28.1 ± 4.8	0.26
Enrolled in the US, %	13.7	13.6	0.19
Clinical characteristics			
Diabetes mellitus, %	27.6	28.3	0.72
Insulin-dependent, %	10.1	9.9	0.90
Current smoker, %	22.0	18.5	0.07
Previous MI, %	33.3	32.1	0.59
Peripheral vascular disease	10.5	9.2	0.36
COPD, %	9.2	7.9	0.34
Prior stroke or TIA, %	9.1	7.7	0.29
History of CHF, %	5.2	4.0	0.27
Angiographic characteristics			
LVEF, %	58.3 ± 13.2	59.1 ± 12.9	0.31
LM disease (any), %	39.4	39.3	0.98
LM only	5.4	4.5	0.98
1 other artery	8.1	7.5	0.36
2 other arteries	12.2	12.4	0.65
3 other arteries	13.7	15.0	0.90
3-vessel disease (no LM), %	60.6	60.7	0.98
SYNTAX Score	29.1 ± 11.3	28.4 ± 11.4	0.21

mITT indicates modified intention to treat; CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; mITT, modified intention-to-treat; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

RESULTS

Patient Population

Overall, a total of 1800 patients with 3-vessel or left main CAD were randomized to either CABG (n = 897) or PCI (n = 903). Of these, 27 patients assigned to CABG and 7 patients assigned to PCI did not undergo any revascularization procedure and were excluded from the primary mITT population for this economic analysis (Figure 1). Baseline characteristics for the mITT population are summarized in Table 1. There were no significant differences in any observed characteristics between the CABG and PCI groups. Of the mITT patients, 13.6% were enrolled in the United States, 39% had left main CAD, and the median follow-up was 60 months.

Initial Treatment Costs

Among patients assigned to PCI, 98.8% underwent PCI and 1.2% underwent CABG. Among patients assigned to CABG, 98.2% underwent CABG and 1.8% underwent PCI. Resource utilization for the initial revascularization procedures is summarized in Table 2

Table 2. Index Procedural Resource Utilization and Cost (per Protocol Population)

	CABG (n=854)	PCI (n=885)	*p*-value
Number of PCI procedures, %			
1	-	85.9 (760/885)	
2	-	13.5 (124/885)	
3 or more	-	0.1 (1/885)	
Procedure duration, minutes	209±62 [205]	101±55 [90]	<0.001
Guiding catheters	-	2.1 ± 1.2	
Guidewires	-	3.5 ± 2.3	
Paclitaxel-eluting stents	-	4.5 ± 2.3	
Bare metal stents	-	0.0 ± 0.3	
Angioplasty balloons	-	3.7 ± 2.8	
Rotablator burrs	-	0.1 ± 0.3	
IVUS catheters	-	0.1 ± 0.4	
Closure device	-	0.4 ± 0.6	
Contrast volume, ml	-	415 ± 207.5 [380]	
Antithrombotic agents used, %			
Bivalrudin	-	7.2% (64/885)	
Abciximab	-	15.6% (138/885)	
Eptifibatide	-	9.5% (84/885)	
Tirofiban	-	10.7% (95/885)	
Index procedure cost, $	8504 ± 1972 [8356]	11,919 ± 6162 [11263]	<0.001

Values in brackets represent medians. CABG, coronary artery bypass grafting; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention.

Table 3. Index Hospitalization Events, Resource Utilization, and Costs (mITT population)

	CABG (n=870)	PCI (n=896)	Difference (95% CI)	*p*-value
Death, %	1.4 (12/870)	1.8 (16/896)	−0.4 (−1.6, 0.8)	0.49
MI, %	2.4 (21/870)	2.7 (24/896)	−0.3 (−1.7, 1.2)	0.72
Stroke, %	1.0 (9/870)	0.1 (1/896)	0.9 (0.2, 1.6)	0.01
Unplanned CABG, %	1.1 (10/870)	0.8 (7/896)	0.4 (−0.5, 1.3)	0.42
Unplanned PCI, %	0.5 (4/870)	1.8 (16/896)	−1.3 (−2.3, −0.3)	0.008
Complications, %				
Major bleeding	4.8 (42/870)	4.5 (40/896)	0.4 (−1.6, 2.3)	0.72
Respiratory failure	1.6 (14/870)	0.0 (0/896)	1.6 (0.8, 2.4)	< 0.001
Renal failure	2.4 (21/870)	0.7 (6/896)	1.7 (0.6, 2.9)	0.003
Wound infection	4.1 (36/870)	0 (0/896)	4.1 (2.8, 5.5)	< 0.001
Other infection	6.2 (54/870)	0.4 (4/896)	5.8 (4.1, 7.4)	< 0.001
Atrial fibrillation	17.9 (156/870)	1.3 (12/896)	16.6 (13.9, 19.2)	< 0.001
Cardiac tamponade	0.8 (7/870)	0.3 (3/896)	0.5 (−0.2, 1.2)	0.22
Other procedures, %				
Permanent pacemaker	0.6 (5/870)	0.2 (2/896)	0.4 (−0.2, 0.9)	0.28
ICD implantation	0.2 (2/870)	0.0 (0/896)	0.2 (−0.1, 0.5)	0.24
Carotid endarterectomy	0.5 (4/870)	0.0 (0/896)	0.5 (0.0, 0.9)	0.06
Initial hospitalization costs, $				
Revascularization procedures	8580 ± 2231 [8340]	12,054 ± 6287 [8340]	−3474 (−3917, −3032)	< 0.001
Hospital stay + ancillary services	19,511 ± 6655 [16,669]	8785 ± 5,464 [6216]	10,726 (10,159, 11,294)	< 0.001
Physician fees	5100 ± 853 [4956]	2315 ± 954.8 [1942]	2785 (2700, 2869)	< 0.001
Total	33,190 ± 7938 [30,903]	23,154 ± 10,379 [20,279]	10,036 (9172, 10,901)	< 0.001

Values in brackets are medians. CCU, cardiac care unit; CI, confidence interval; ICD, implantable cardioverter-defribillator; ICU, intensive care unit; mITT, modified intention-to-treat.

(PP population). In the PCI group, 13.6% underwent staged procedures, with 13.5% requiring 2 procedures and 0.1% requiring 3 procedures. On average, the initial PCI procedure required 2.1 guiding catheters, 3.5 guidewires, 3.7 angioplasty balloons, and 4.5 drug-eluting stents. Although procedure duration was longer for CABG, initial procedure costs were ~$3500 lower with CABG as compared with PCI ($8504 vs. $11,919, $p < 0.001$), owing to the higher costs associated with consumable resources (including stents) for the PCI group. For the mITT population, the difference in initial procedural costs was slightly smaller ($8482 vs. $11,866, $p < 0.001$), as a result of the small proportion of patients who crossed over to the alternative treatment strategy.

Clinical events, resource utilization, and costs during the initial hospitalization are summarized in Table 3. Post-procedural hospital costs were greater for the CABG group than the PCI group ($19,511 vs. $8785, $p < 0.001$), as were physician fees ($5100 vs. $2315, $p < 0.001$). As a result, total initial hospitalization costs were ~$10,000/patient higher in the CABG group than in the PCI group ($33,190 vs. $23,154, $p < 0.001$).

Follow-up Resource Utilization and Costs

Follow-up clinical outcomes, resource utilization, and costs are summarized in Table 4. During each year of follow-up, the annual rates of repeat revascularization, diagnostic catheterization, hospitalization, and their associated costs were higher for the PCI group as compared with the CABG group. In addition, costs for outpatient services and medications were consistently higher for patients assigned to initial PCI vs. CABG. Rehabilitation costs were greater in the CABG group in the first year and were similar between treatments in the subsequent years. As a result, the difference in cumulative medical care costs between the CABG and PCI narrowed from $10,036 after the index hospitalization to $5619 after 5 years of follow-up (Table 5 and Figure 2).

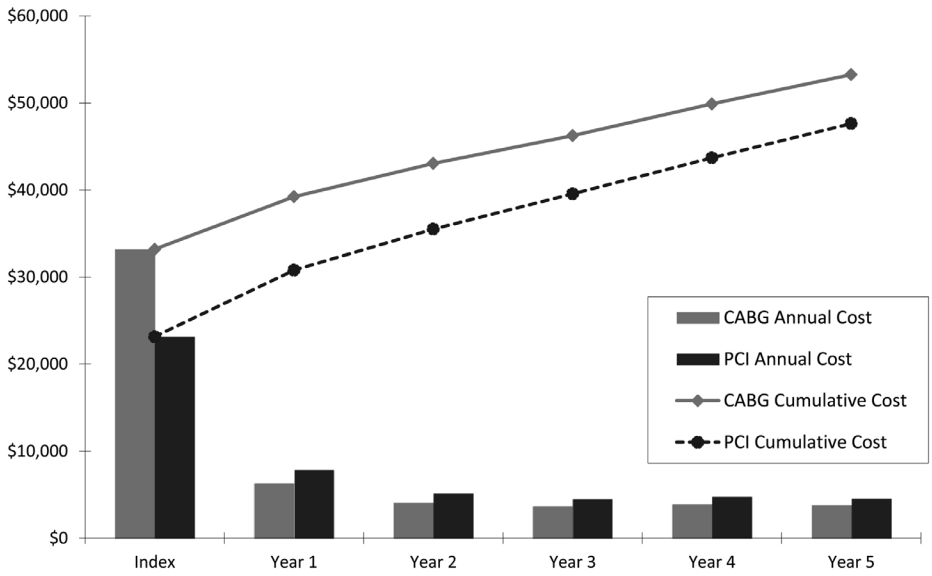

Figure 2.
Mean cumulative medical costs (lines) and mean annual follow-up costs (bars) in 2010 dollars, for the PCI and CABG groups. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. Note that the first set of bars represent represents the costs of the index hospitalization.

Table 4. Follow-Up Events, Resource Utilization, and Costs (mITT population)

	Year 1		Year 2		Year 3		Year 4		Year 5		5-year Cumulative		
	CABG n=870	PCI N=896	CABG n=813	PCI N=851	CABG n=791	PCI N=832	CABG n=767	PCI N=805	CABG n=733	PCI N=771	CABG n=870	PCI N=896	*p*-value
Clinical outcomes													
Death, %	1.8	2.6	1.5	2.0	1.9	2.6	2.2	3.2	2.9	2.3	10.7	13.6	0.06
MI, %	0.9	2.2	0.1	1.2	0.3	1.2	0.3	1.7	0.0	1.2	3.7	9.3	<0.001
Stroke, %	1.0	0.6	0.7	0.7	0.5	0.6	0.4	0.2	0.0	0.1	3.4	2.2	0.12
Resource use (events/100 pts)													
Repeat revascularization (any)	4.8	14.1	3.9	6.6	2.5	3.7	2.2	5.5	2.6	4.3	16.6	35.2	<0.001
PCI procedures	4.7	11.9	3.9	5.6	2.5	2.8	2.2	4.8	2.6	3.1	15.3	28.9	<0.001
CABG procedures	0.1	2.1	0.0	0.9	0.0	1.0	0.0	0.6	0.0	1.2	1.3	6.3	<0.001
Diagnostic catheterization	3.8	11.6	2.3	6.5	1.9	4.1	0.1	0.2	1.4	3.4	10.1	22.3	<0.001
Re-hospitalization	27.7	41.1	16.6	20.9	12.9	15.6	14.5	18.3	11.5	13.5	77.5	103.6	<0.001
Cost per patient, $													
Rehospitalizations	2435	3964	1570	2044	1200	1485	1240	1664	1178	1471	-	-	-
Outpatient services	323	333	91	167	83	110	141	171	118	165	-	-	-
Rehab/skilled nursing stays	900	186	27	14	28	15	30	47	31	49	-	-	-
Medications	1578	2136	1787	2186	1837	2236	1866	2204	1952	2300	-	-	-
MD fees	724	1027	439	558	348	421	384	446	321	381	-	-	-
Total	5959	7646	3914	4970	3495	4266	3661	4532	3601	4366	-	-	-

CABG; coronary artery bypass grafting; MI, myocardial infarction; mITT, modified intention-to-treat; PCI, percutaneous coronary intervention

Utility Weights and QALYs

Compared with baseline, utility weights improved substantially for both treatment groups over the course of the trial (Supplementary Table 5). At 1 month follow-up, utility weights were significantly lower after CABG than PCI (0.77 vs. 0.85, $p < 0.001$), reflecting the longer recovery period following CABG. This early utility benefit of PCI was no longer apparent at 6 months, however. As a result of the early difference in favor of PCI, cumulative quality-adjusted life-years were lower with CABG than with PCI through 3 years of follow-up (Table 5). By the end of year 5, however, life expectancy (4.70 vs. 4.60 years) and quality-adjusted life expectancy (3.91 vs. 3.87 QALYs) were both greater with CABG than with PCI.

Table 5. Cumulative Costs, QALYs, and Life-Years for Years 1 to 5, Adjusted for Censoring

Time Since Randomization	Cumulative Costs, $			Cumulative QALYs			Cumulative Life-Years		
	CABG	PCI	Δ	CABG	PCI	Δ	CABG	PCI	Δ
1 year	39,241	30,797	8444	0.789	0.813	−0.025	0.975	0.965	0.009
2 years	43,053	35,520	7533	1.595	1.614	−0.018	1.933	1.912	0.022
3 years	46,428	39,567	6862	2.394	2.396	−0.002	2.877	2.832	0.045
4 years	49,890	43,702	6188	3.166	3.148	0.019	3.800	3.732	0.069
5 years	53,260	47,641	5619	3.914	3.870	0.044	4.701	4.601	0.100

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-years gained. Δ=difference between CABG and PCI group; Δ, difference between CABG and PCI group

Lifetime Cost-Effectiveness - Overall Population

Results from the lifetime cost-effectiveness analyses are summarized in Table 6. Based on the observed 5-year results, the estimated mortality hazard ratio for CABG vs. PCI was 0.80 (95% CI, 0.61-1.05). When these results were used to project clinical and economic outcomes beyond the trial period (Figure 3), we estimated that CABG would be associated with lifetime incremental costs of $5081 (95%CI, $1802 to $8241) compared with PCI together with a gain in life expectancy of 0.412 years (95% CI, −0.060 to 0.831) and a gain in quality-adjusted life expectancy of 0.307 QALYs (95% CI, −0.105 to 0.378).

The resulting incremental cost-effectiveness ratio (ICER) for CABG vs. PCI was $16,537/QALY gained, with 84.7% of bootstrap replicates falling below a societal willingness-to-pay threshold of $50,000/QALY (Figures 4 and 5, and Table 6/row 1). When outcomes were assessed in life-years, CABG was associated with an ICER of $12,329/life-year gained (Table 6/row 2). When the analysis also accounted for the prognostic impact of non-fatal MI and stroke, the benefit of CABG increased modestly to 0.338 QALYs, and the ICER improved to $15,758/QALY gained with 87.7% of bootstrap replicates falling below a societal willingness-to-pay threshold of $50,000/QALY (Figure 5, Table 6/row 4).

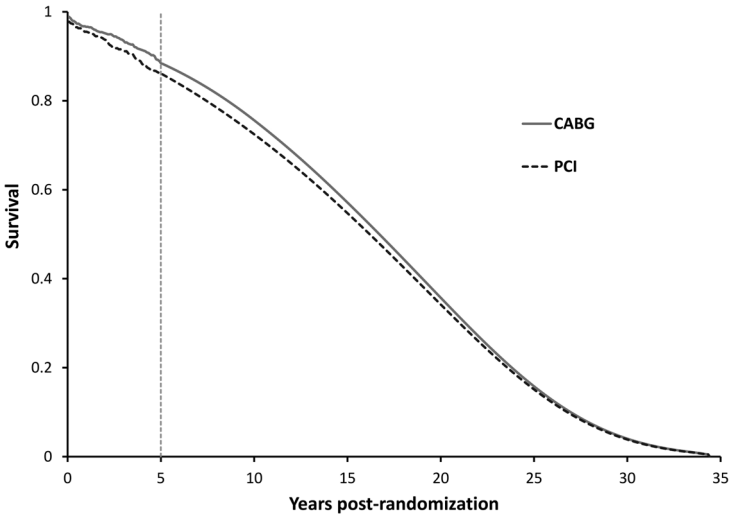

Figure 3.
Observed survival through 5 years and predicted survival beyond 5 years for the CABG and PCI groups, according to the base case assumptions. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

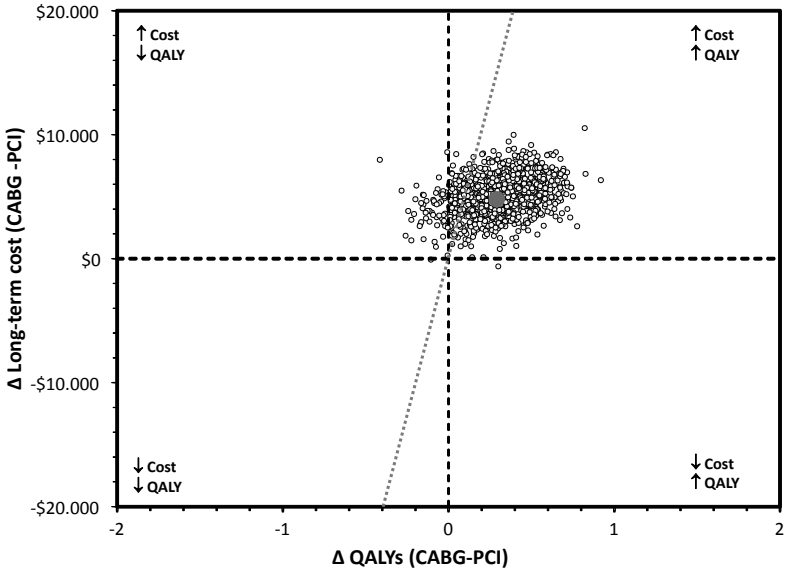

Figure 4.
Joint distribution of projected lifetime incremental costs and quality-adjusted life expectancy for CABG vs. PCI based on bootstrap replication of the SYNTAX trial population, plotted on the cost-effectiveness plane. The black circle represents the estimated mean values (incremental cost=$5081, incremental QALYs=0.307). CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year.

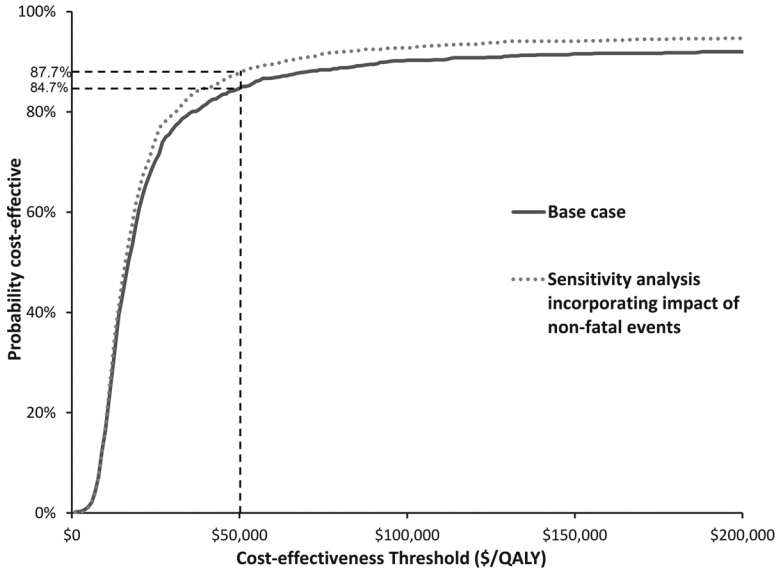

Figure 5.
Cost effectiveness acceptability curve of CABG vs. PCI. The probability that CABG is cost-effective is calculated as the proportion of bootstrap-derived estimates falling below a given cost-effectiveness threshold and is plotted across a range of possible cost-effectiveness thresholds. The solid blue line represents the base-case analysis, while the dashed red line indicates the analysis in which the prognostic impact of MI and stroke were taken into account.

These results were robust across a wide range of alternative assumptions regarding the duration and magnitude of the benefit of CABG over PCI on both survival and costs beyond the timeframe observed in the trial. When we assumed that the benefits of CABG would remain constant from year 5 to year 10, with no further benefit beyond 10 years, the ICER for CABG vs. PCI improved to $10,695/QALY gained. Under the conservative assumption of no benefit of CABG beyond the 5-year trial period, the ICER increased to $27,485/QALY gained with 74.8% of the bootstrap replicates below the $50,000 per QALY gained threshold. Results were also similar when the analysis incorporated the prognostic impact of non-fatal MI and stroke, or when effectiveness was expressed in life-years rather than QALYs (Supplementary Tables 7 and 8).

Subgroup Analyses

Results from prespecified, subgroup analyses are summarized in Supplementary Table 6 (observed 5-year results) and Table 7 (lifetime projections). For most subgroups, the results were consistent with those of the overall trial population albeit with greater uncertainty due to the reduced sample sizes. There were 2 subgroups with results that differed substantially from those of the overall trial, however. For patients with less complex coronary anatomy (SYNTAX Score ≤22), PCI was projected to improve increase

Table 6. Lifetime Cost-Effectiveness Results for Base Case and Sensitivity Analyses

	Cost, $			QALYs			ICER ($/QALY)	% Dominant	% Dominated	%<$50K
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)				
Tapered CABG effect between 5 and 10 years										
Base case lifetime analysis	92,509	87,428	5081 (1802, 8241)	10.544	10.237	0.307 (−0.105, 0.678)	16,537	0.1	5.8	84.7
Life-years instead of QALYs*	92,509	87,428	5081 (1802, 8241)	12.508*	12.096*	0.412 (−0.060, 0.831)*	12,329*	0.1	3.7	91.9
Undiscounted cost and QALYs	113,412	108,428	4984 (852, 8802)	14.619	14.127	0.492 (−0.093, 1.027)	10,139	0.5	4.0	92.0
Incorporate prognostic effect of MI and Stroke	91,569	86,239	5331 (2264, 8368)	10.455	10.117	0.338 (−0.077, 0.705)	15,758	0.0	4.5	87.7
Fixed CABG effect between 5 and 10 years										
Lifetime analysis	91,608	87,428	4180 (672, 7483)	10.627	10.237	0.391 (−0.140, 0.853)	10,695	0.9	5.3	89.1
Life-years instead of QALYs*	91,608	87,428	4180 (672, 7483)	12.607*	12.096*	0.512 (−0.093, 1.026)*	8171*	0.9	3.5	93.3
Undiscounted cost and QALYs	112,369	108,428	3941 (−614, 7922)	14.750	14.127	0.623 (−0.114, 1.295)	6327	3.0	3.0	91.7
Incorporate prognostic effect of MI and Stroke	90,687	86,239	4448 (1066, 7642)	10.539	10.117	0.423 (−0.097, 0.874)	10,523	0.5	4.2	91.3
No effect of CABG beyond 5 years										
Lifetime analysis	93,510	87,428	6082 (3046, 9064)	10.458	10.237	0.221 (−0.091, 0.511)	27,485	0.0	6.7	74.8
Life-years instead of QALYs*	93,510	87,428	6082 (3046, 9064)	12.405*	12.096*	0.310 (−0.047, 0.633)*	19,639*	0.0	3.4	87.4
Undiscounted cost and QALYs	114,522	108,428	6094 (2372, 9793)	14.489	14.127	0.362 (−0.067, 0.780)	16,848	0.1	4.9	87.6
Incorporate prognostic effect of MI and Stroke	92,550	86,239	6311 (3535, 9163)	10.368	10.117	0.251 (−0.052, 0.539)	25,149	0.0	4.6	79.6

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year gained. Costs, life-years and QALYs are discounted at 3% per year

*Results in this row represent life-years (instead of QALYs) and cost per life-year gained (instead of cost per QALY gained)

Table 7. Lifetime Cost-Effectiveness Results for Subgroups

	Cost, $			QALYs			ICER ($/QALY)	% CABG Dominant	% CABG Dominated	%CABG <$50K*
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)				
Age ≤60 (n=553)	105,305	101,926	3378 (−3261, 9692)	14.28	13.95	0.32 (0.40, 0.95)	10,488	7.7	11.1	72.3
Age 61-70 (n=586)	92,881	88,303	4578 (−1070, 10581)	10.55	10.21	0.34 (−0.44, 1.00)	13,359	3.6	14.5	74.0
Age >70 (n=627)	80,810	73,555	7254 (1972, 12302)	7.19	6.97	0.21 (−0.51, 0.84)	34,027	0.1	25.5	57.6
Diabetes (n=494)	97,787	91,943	5843 (−378, 12214)	10.12	9.53	0.59 (−0.15, 1.28)	9864	2.6	6.1	87.7
No diabetes (n=1272)	90,383	85,644	4739 (908, 8519)	10.68	10.52	0.16 (−0.323, 0.606)	29,129	0.1	24.1	64.2
LM disease (n=694)	93,732	86,114	7618 (2225, 12734)	9.94	10.233	−0.29 (−1.00, 0.37)	PCI dominant	0.0	81.1	8.9
3-vessel disease (n=1072)	91,619	88,270	3350 (−673, 7368)	10.92	10.24	0.68 (0.17, 1.10)	4905	5.2	0.2	94.3
SYNTAX Score ≤22 (n=562)	95,624	92,582	3043 (−2826, 9205)	10.97	11.17	−0.20 (−0.95, 0.46)	PCI Dominant	1.8	60.6	18.3
SYNTAX Score 23-32 (n=600)	87,747	83,540	4207 (−1432, 9544)	10.29	10.18	0.114(−0.60, 0.79)	36,790	2.0	32.8	52.3
SYNTAX Score ≥33 (n=595)	94,309	86,384	7925 (2740, 13296)	10.36	9.40	0.96 (0.35, 1.58)	8219	0.2	0.2	99.4
US patients (n=241)	105,396	96,015	9382 (−1623, 20402)	10.84	10.05	0.79 (−0.30, 1.78)	11,936	3.1	5.4	85.7
Non-US patients (n=1525)	90,500	86,086	4414 (1027, 7601)	10.50	10.27	0.24 (−0.20, 0.65)	18,737	0.2	13.3	75.7

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio for CABG vs. PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year gained; LM, left main;

* Probability that CABG is the preferred strategy at a societal ICER of $50,000/QALY gained

Costs and QALYs are discounted at 3% per year.

quality-adjusted life expectancy and to reduce costs compared with CABG. For this subgroup, the probability that CABG would be economically attractive at an ICER of $50,000/QALY was only 18.3%. In contrast, for patients with SYNTAX Scores of 23-32 and ≥33, the ICERs for CABG vs. PCI were $36,790/QALY gained and $8219/QALY gained, respectively. PCI was also projected to be an economically dominant strategy for patients with left main CAD, whereas CABG appeared to be highly economically attractive compared with PCI for patients with 3-vessel disease (ICER $4905/QALY gained). For all other patient subgroups, CABG was projected to be economically attractive compared with PCI with ICERs <$35,000/QALY gained. Results for subgroups were largely unchanged under alternative assumptions regarding the duration and magnitude of the benefit of CABG over PCI, and when we considered the impact of non-fatal MI and stroke on mortality (Supplementary Tables 7 and 9).

Impact of Stent Pricing and Productivity Losses

Since DES prices in the US continue to decrease each year, we performed a sensitivity analysis on the acquisition cost of DES (Figure 6). Although the ICER for CABG vs. PCI increased as the acquisition cost of DES decreased, even at a DES price of $0, the ICER for CABG vs. PCI in the overall study population remained <$40,000/QALY gained. When this sensitivity analysis was repeated within strata according to SYNTAX Score, only the intermediate SYNTAX Score tertile was sensitive to stent price (Supplementary Table 10).

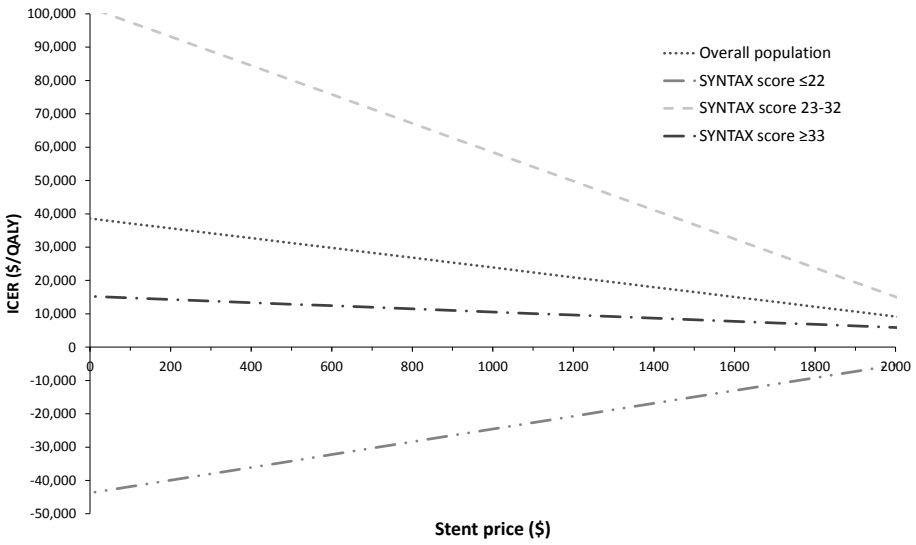

Figure 6.
Sensitivity analysis of the ICER for CABG vs. PCI as a function of the stent price in the overall population and according to the anatomic SYNTAX Score. The negative ICERs for the low SYNTAX Score population indicate that PCI was economically dominant over the full range of stent prices displayed.

For patients with a SYNTAX Score ≤22, the PCI strategy remained economically attractive unless the stent price exceeded $4880/stent, while for patients with a SYNTAX Score ≥33, CABG remained economically attractive at all stent prices. Among patients with SYNTAX Scores between 23 and 32, however, the ICER for CABG vs. PCI remained <$50,000/QALY gained only if the stent price were >$1195.

Finally, we performed a sensitivity analysis to assess the impact of productivity loss on the cost-effectiveness of CABG vs. DES-PCI. Since no data on employment were collected from the SYNTAX trial patients, we used several external sources to estimate the proportion of patients employed at baseline, the timing of return to work according to the type of revascularization procedure, and the average earning for a US worker.[9, 29] With incorporation of these factors, the cost difference between the treatments increased by ~$1000 for the overall population, reflecting the higher productivity loss with CABG compared to PCI, but the ICER for CABG vs. PCI remained <$20,000/QALY gained (Supplementary Table 11). When this additional analysis was repeated for subgroups according to SYNTAX Score tertile and LM or 3-vessel disease subgroups, the outcomes were similar to the main analyses that did not incorporate productivity losses.

DISCUSSION

SYNTAX is the first study to directly compare the long-term clinical and economic outcomes of DES-PCI vs. CABG for patients with 3-vessel or left main CAD. As such, this economic substudy provides a number of critical insights about the optimal revascularization strategy for such patients. First, we found that despite substantially higher procedural costs, DES-PCI is substantially less costly than CABG in the short term. Second, although CABG was associated with improved clinical outcomes and reduced follow-up resource utilization, cumulative costs remained lower with DES-PCI (by ~$5000/patient) at 5 years and over a lifetime horizon. Third, although differences in life expectancy and quality-adjusted life expectancy were small over the 5-year timeframe of the trial (0.100 years and 0.044 QALYs, respectively), the incremental life expectancy and QALY gains with CABG increased considerably when projected over a patient's lifetime. As a result, the lifetime incremental cost-effectiveness ratio for CABG vs. DES-PCI was ~$16,500/QALY gained and ~$12,500/LY gained—values that compare favorably with many other accepted therapies in the context of the US healthcare system.[30, 31] Moreover, while SYNTAX did not demonstrate a "statistically significant" difference in 5-year mortality between CABG and DES-PCI, these main findings were robust to both stochastic uncertainty analyses (i.e., bootstrapping) and to a variety of alternative assumptions regarding the durability of benefit, the prognostic impact of

non-fatal events, and stent pricing. In general, the economic outcomes of the SYNTAX trial mirrored the clinical results.

Although the results of the overall trial were robust, subgroup analyses demonstrated several key cohorts with results that diverged from those of the main SYNTAX population. Specifically, among patients with left main disease or SYNTAX Score ≤22, DES-PCI was projected to be an economically dominant strategy that resulted in similar or greater quality-adjusted life expectancy and lower lifetime costs compared with CABG. Although these results were not definitive (due mainly to uncertainty with respect to long-term survival differences), these findings suggest that DES-PCI may be the preferred strategy for patients with less anatomically complex CAD on both clinical and economic grounds. In contrast, among patients with 3-vessel disease or with anatomic SYNTAX Scores ≥32, CABG was strongly favored on economic grounds with ICERs <$10,000/QALY gained and a <6% probability that the ICER exceeds $50,000/QALY gained. While subgroup analyses are typically considered "hypothesis generating" when interpreting clinical trial results, cost-effectiveness analysis is driven by measures of absolute cost and benefit that may be more susceptible to meaningful interactions. As such, subgroup effects in cost-effectiveness analysis are frequently considered to be valid considerations for guideline development and health care policy—particularly when the results are supported by appropriate uncertainty analyses and are consistent with the underlying pathophysiology.[32]

The finding that our results were only minimally sensitive to stent pricing was somewhat surprising. Although device prices are commonly perceived to be an important determinant of their cost-effectiveness,[33] when comparing DES-PCI vs. CABG, we found that the major determinant of cost-effectiveness was the gain in life expectancy rather than the cost difference, per se. Consequently, there was no device cost at which DES-PCI would be economically attractive compared with CABG in either the overall trial population or in patients with a high SYNTAX Score. Only among patients with an intermediate SYNTAX Score (where the gain in quality-adjusted life expectancy with CABG was minimal) would DES-PCI become the economically preferred therapy if the device cost were reduced by ~20% from current levels.

Comparison with Previous Studies

These findings contrast with those from our previous cost-effectiveness analysis of DES-PCI vs. CABG based on the 1-year SYNTAX trial results, in which we reported that DES-PCI was an economically dominant strategy.[34] Compared with that previous report, the initial cost difference in favor of DES-PCI has increased from ~$5000/patient to ~$10,000/patient—changes driven largely by the substantial reduction in DES prices over the last 4-5 years (from $2200/stent to $1500/stent). Another important difference between

the 2 studies is the cost difference in the first year of follow-up, which decreased from ~$2300 in the original study to ~$1700 in the current study— due mainly to reductions in the cost of dual antiplatelet therapy with the approval of generic clopidogrel. The most important difference between the 2 studies was that in the 1-year study, quality-adjusted life expectancy favored DES-PCI (reflecting the early QOL and survival advantage), whereas in the current study, quality-adjusted life expectancy was greater with CABG. These differences highlight the importance of basing policy decisions on clinical trials with sufficiently long follow-up to allow prognostically important benefits to emerge. Although many third-party payers in the US are more concerned with a 1-3 year time horizon than a lifetime horizon, the results of our study demonstrate how analyses that focus solely on short-term economic and clinical outcomes may fail to incorporate the full benefits of the more effective therapy and arrive at misleading conclusions.

Numerous previous studies have sought to evaluate the relative cost-effectiveness of PCI vs. CABG for patients with multivessel CAD.[7, 9, 15, 28, 35-39] However, most of these studies are limited by relatively short follow-up durations,[7, 34, 36, 39] or by focusing solely on costs without performance of a formal cost-effectiveness analysis.[35] In addition, no studies to date have examined the cost-effectiveness of PCI vs. CABG for patients with left main disease. With respect to methodology and duration of follow-up, our study is most comparable to economic evaluations performed alongside the BARI and FREEDOM trials. In BARI, the ICER for CABG vs. balloon angioplasty was ~$14,000/life-year gained over a 12 year follow-up period[28]—results that are quite similar to those from the SYNTAX trial. In contrast to SYNTAX, however, BARI found that for patients with 3-vessel CAD costs were actually lower with CABG than PCI over 5 years of follow-up.[9] It is likely that these differences between trials reflect the much lower rate of repeat revascularization procedures after PCI seen in SYNTAX as compared with BARI with the introduction of effective drug-eluting stents (26% vs. 54%).[3, 12]

FREEDOM is the only other trial to compare the cost-effectiveness of PCI vs. CABG in the DES era and demonstrated that for patients with diabetes and multivessel CAD, CABG is highly cost-effective compared with DES-PCI with an ICER of ~$8000/QALY gained.[15] Although these overall results are relatively similar to those seen in SYNTAX, in FREEDOM CABG was economically attractive across the full range of SYNTAX Scores whereas in SYNTAX, CABG was only attractive for patients moderate to high degrees of angiographic complexity (SYNTAX Score >22). These findings may relate to underlying differences in atherosclerosis between patients with vs. without diabetes or may reflect the fact that diabetic patients often have additional conditions (e.g. renal dysfunction, peripheral artery disease) that confer higher cardiovascular risk.[13] Of note, patients with left main coronary disease were not studied in either BARI or FREEDOM.

Limitations

Our study has several important limitations. First, our economic analysis was performed from the perspective of the U.S. healthcare system, although the SYNTAX trial enrolled patients from 18 countries. To address this issue, costs associated with the index procedures were estimated from detailed resource use, which would not be expected to differ by geography. Since hospital length of stay differs across countries, all other costs were estimated using methods that were independent of length of stay and depend only the assumption that clinical outcomes and procedural complications are similar across healthcare systems.[40] Although it would have been possible to exclude all non-US patients from our analysis, this would have markedly reduced our sample size and added considerable variability to the results. It is nonetheless reassuring that our main results were consistent between patients enrolled in the US compared with other countries.

Second, the need for lifetime extrapolations required several assumptions regarding the impact of CABG on long-term survival, health care costs, and quality-of-life. To the greatest extent possible, we used empirical data from the trial to inform these assumptions and examined the impact of plausible alternatives in sensitivity analyses, the results of which were similar to our primary results. Third, all DES patients in the SYNTAX trial were treated with paclitaxel-eluting DES. Recently, second-generation DES have demonstrated lower rates of MI, target vessel revascularization, and stent thrombosis as compared with first-generation DES.[41] Therefore, the cost results of the current study may not be generalizable to patients treated with second-generation DES. It is unlikely that the main results of our analysis would change substantially with use of second generation DES, however, since there is no evidence that these devices reduce mortality compared with the paclitaxel-eluting stents that were used in SYNTAX.[41] Finally, PCI in the SYNTAX trial did not incorporate routine use of physiologic guidance—a technique that has recently been shown to both improve clinical outcomes and lower long-term costs compared with angiographic guidance.[42, 43] Future trials comparing physiologically-guided PCI vs. CABG will be required to determine the overall cost-effectiveness of this strategy.

Conclusions

Based on the results of the SYNTAX trial, for most patients with 3-vessel or left main CAD without recent MI, CABG is a clinically and economically attractive revascularization strategy compared with DES-PCI. However, among patients with less complex disease, DES-PCI may be preferred on both clinical and economic grounds. These findings provide additional support for existing guidelines and underscore the importance of ongoing studies to define the optimal revascularization strategy for patients with left main disease.

ACKNOWLEDGEMENTS

We thank Kristine Roy for her administrative assistance and Randall Richner and Mary Ann Clark for their assistance in the design of the study.

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APPENDIX

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Supplementary Table 1. Linear Regression Models developed from MedPAR Data for the Prediction of Post-Procedure Costs

Model variable	CABG (n=43,866)	PCI (n=113,921)
Intercept* (uncomplicated hospitalization, non-procedure costs)	16,669	6216
Demographics		
Age≥80 years	2209	170
Female	671	−8
Co-morbidities		
Congestive heart failure	3294	1752
COPD	−340	614
Chronic renal failure, without dialysis	−850	226
Chronic renal failure, with dialysis	9569	3192
Gastro-intestinal bleeding	-	1673
Complications		
Death	12,519	3200
Stroke	9674	6580
Myocardial infarction	9688	6258
Additional PCI	11,070	9285
Additional CABG	-	21,992
Major vascular complication	8457	2541
Transfusion	-	3829
Cardiogenic shock	16,739	7002
Post-operative hypotension	-	1308
Respiratory failure	9009	9946
Renal failure	10,068	5477
Post-operative infection	14,802	9211
Post-operative atrial fibrillation	903	2861
Post-operative ventricular arrhythmia	-	3316
Pacemaker insertion	10,087	5984
Cardiac Tamponade	7555	6122
Pulmonary embolus	9717	8975
R^2	0.21	0.18

The impact of interactions for age with complications was tested, but did not improve the model. *Intercepts haven been adjusted to exclude the cost of otherwise uncomplicated procedures. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention

Supplementary Table 2. Linear Regression Models developed from MedPAR Data for the Prediction of Post-Procedure Length of Stay

Model variable	CABG (n=43,866)	PCI (n=113,921)
Intercept* (uncomplicated hospitalization, non-procedure costs)	6.79	1.61
Demographics		
Age≥80 years	0.94	0.23
Female	0.81	0.31
Co-morbidities		
Congestive heart failure	1.50	1.35
COPD	0.14	0.46
Chronic renal failure, without dialysis	−0.01	0.43
Chronic renal failure, with dialysis	3.18	1.46
Gastro-intestinal bleeding	-	1.46
Complications		
Death	0.07	−0.34
Stroke	4.33	3.07
Myocardial infarction	3.05	2.53
Additional PCI	1.03	1.52
Additional CABG	-	5.34
Major vascular complication	1.81	1.09
Transfusion	-	2.31
Cardiogenic shock	3.29	2.37
Post-operative hypotension	-	0.22
Respiratory failure	2.99	4.33
Renal failure	4.29	3.80
Post-operative infection	7.92	5.10
Post-operative atrial fibrillation	0.61	1.62
Post-operative ventricular arrhythmia	-	1.63
Pacemaker insertion	1.98	0.95
Cardiac Tamponade	3.70	1.01
Pulmonary embolus	4.39	4.68
R^2	0.21	0.27

The impact of interactions for age with complications was tested, but did not improve the model. *Intercepts haven been adjusted to exclude the cost of otherwise uncomplicated procedures. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Supplementary Table 3. Regression Model developed from SYNTAX Follow-Up Cost for the Prediction of Long-Term costs

Parameter	Coefficient Estimate ($)	*p*-value
Intercept	4367	<0.001
CABG	−897	<0.001
Age	5	0.586
Male	−655	0.003
SYNTAX Score 23-32	−486	0.029
SYNTAX Score ≥33	−190	0.396
Left main disease	329	0.077
Peripheral vascular disease	2449	<0.001
Myocardial Infarction during trial	3807	<0.001
Stroke during trial	3898	<0.001

Supplementary Table 4. Regression Model developed from SYNTAX Follow-Up Utility data for the Prediction of Long-Term Utility Weights

Parameter	Coefficient Estimate	*p*-value
Intercept	0.78900	<0.001
Male	0.08641	<0.001
SYNTAX Score 23-32	0.00058821	0.894
SYNTAX Score ≥33	−0.01156	0.009
History of Stroke	−0.02188	0.001
Peripheral vascular disease	−0.03754	<0.001
Carotid artery disease	−0.03080	<0.001
Myocardial Infarction during trial	−0.01542	0.086
Stroke during trial	−0.08218	<0.001

Supplementary Table 5. EQ-5D Utility Scores by Treatment Assignment

Timepoint	CABG	PCI	*p*-value
Baseline	0.741 ± 0.191 [0.800]	0.754 ± 0.187 [0.800]	
1 month	0.769 ± 0.171 [0.816]	0.853 ± 0.156 [0.844]	<0.001
6 months	0.847 ± 0.153 [0.827]	0.862 ± 0.150 [0.844]	0.09
12 months	0.850 ± 0.158 [0.827]	0.854 ± 0.157 [0.844]	0.98
36 months	0.850 ± 0.161 [0.843]	0.847 ± 0.164 [0.833]	0.62
60 months	0.846 ± 0.173 [0.838]	0.843 ± 0.174 [0.843]	0.83

Values in brackets are medians. CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. *P*-values are derived from ANCOVA, adjusted for baseline.

Supplementary Table 6. In-trial 5-Year cumulative costs, QALYs, and Life Years

Population	Hazard Ratio (95% CI)	Cumulative Costs, $			Cumulative QALYs			Cumulative life years		
		CABG	PCI	Δ (95% CI)	CABG	PCI	Δ (95% CI)	CABG	PCI	Δ (95% CI)
Overall (n=1766)	0.800(0.611,1.048)	53,260	47,641	5,619 (3,242,7925)	3.914	3.870	0.044 (−0.066, 0.153)	4.701	4.601	0.100 (−0.05, 0.198)
Age ≤60 (n=553)	0.701(0.335,1.467)	50,752	46,207	4,545 (866, 8267)	4.065	4.057	0.008 (−0.143, 0.161)	4.879	4.820	0.059 (−0.066, 0.183)
Age 61-70 (n=586)	0.726(0.433,1.216)	53,549	48,230	5,319 (2518, 10133)	4.040	3.988	0.052 (−0.115, 0.239)	4.739	4.669	0.070 (−0.103, 0.231)
Age >70 (n=627)	0.883(0.621,1.253)	55,314	48,296	7,018 (3231, 11216)	3.654	3.600	0.054 (−0.140, 0.268)	4.499	4.351	0.148 (−.080, 0.372)
Diabetes (n=494)	0.660(0.421,1.035)	57,677	54,965	2,712 (−1700, 7055)	3.696	3.596	0.010 (−0.114,0.326)	4.586	4.386	0.201 (−0.037, 0.443)
No diabetes (n=1272)	0.896(0.639,1.257)	51,572	44,786	6,785 (4227, 9178)	3.997	3.977	0.020 (−0.096, 0.134)	4.745	4.686	0.059 (−0.046, 0.161)
LM disease (n=694)	1.139(0.755,1.718)	54,839	45,740	9,099 (5213, 12781)	3.803	3.904	−0.101 (−0.265, 0.076)	4.624	4.642	−0.018 (−0.182, 0.149)
3-vessel disease (n=1072)	0.613(0.426,0.883)	52,226	48,871	3,355 (484, 6018)	3.987	3.848	0.139 (−0.001, 0.278)	4.751	4.575	0.176 (0.039, 0.302)
SYNTAX Score ≤22 (n=562)	1.100(0.635,1.905)	53,736	45,486	8,250 (3,665, 12625)	3.899	4.023	−0.124 (−0.298, 0.048)	4.712	4.750	−0.038 (−0.199, 0.118)
SYNTAX Score 23-32 (n=600)	0.946(0.606,1.477)	51,743	47,467	4,276 (684, 7862)	3.904	3.880	0.024 (−0.159, 0.214)	4.645	4.625	0.020 (−0.153, 0.206)
SYNTAX Score ≥33 (n=595)	0.540(0.349,0.837)	54,350	49,910	4,440 (365, 8424)	3.933	3.702	0.231 (0.034, 0.424)	4.742	4.419	0.323 (0.141, 0.524)
US patients (n=241)	0.553(0.246,1.240)	63,363	51,306	12,058 (4308, 19849)	3.959	3.802	0.157 (−0.132, 0.447)	4.803	4.540	0.263 (−.002, 0.550)
Non-US patients (n=1525)	0.839(0.630,1.118)	51,742	47,076	4666 (2282, 7092)	3.907	3.881	0.026 (−0.086, 0.139)	4.685	4.611	0.074 (−.037, 0.178)

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-years gained. Δ=difference between CABG and PCI group; Δ, difference between CABG and PCI group

Supplementary Table 7. Lifetime Cost-Effectiveness Results, incorporating the Impact of MI and Stroke

	Cost, $			QALYs			ICER ($/QALY)	% Dominant	% Dominated	%<$50K
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)				
Base case lifetime analysis (n=1766)	91,569	86,239	5331 (2264, 8368)	10.455	10.117	0.338 (−0.077, 0.705)	15,758	0.0	4.5	87.7
LM disease (n=694)	92,595	85,101	7494 (2493, 12499)	9.840	10.132	−0.292 (−1.00, 0,380)	PCI dominant	0.0	80.3	9.1
3-vessel disease, no LM (n=1072)	90,803	86,967	3836 (−29, 7644)	10.842	10.106	0.735 (0.238, 1.170)	5217	2.5	0.1	97.3
SYNTAX Score ≤22 (n=562)	94,713	91,273	3440 (−2140, 9310)	10.885	11.050	−0.165 (−0.930, 0.508)	PCI dominant	1.3	59.5	21.6
SYNTAX Score 23-32 (n=600)	86,828	82,456	4372 (−1005, 9338)	10.205	10.062	0.143 (−0.600, 0.825)	30,558	1.8	31.2	55.5
SYNTAX Score ≥33 (n=595)	93,310	85,186	8125 (3270, 13131)	10.264	9.273	0.991 (0.359, 1.612)	8125	0.2	0.4	99.1

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio; LM, left main; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year gained. Costs and QALYs are discounted at 3% per year.

Supplementary Table 8. Lifetime Cost-Effectiveness Results for Base Case and Sensitivity Analyses, expressed in Terms of Cost per Life Year gained (instead of QALY)

	Cost, $			LYs			ICER ($/LY)	% Dominant	% Dominated	%<$50K
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)				
Tapered CABG effect between 5 and 10 y										
Life-years instead of QALYs	92,509	87,428	5081 (1802, 8241)	12.508	12.096	0.412 (−0.060, 0.831)	12,329	0.1	3.7	91.9
Undiscounted cost and QALYs	113,412	108,428	4984 (852, 8802)	17.310	16.680	0.629 (−0.042, 1,244)	7921	0.5	3.1	91.9
MI and stroke taken into account	91,569	86,239	5331 (2264, 8368)	12.395	11.949	0.446 (−0.025, 0.872)	11,964	0.0	3.2	94.1
Fixed CABG effect between 5 and 10 y, then HR=1										
Life-years instead of QALYs	91,608	87,428	4180 (672, 7483)	12.607	12.096	0.512 (−0.093, 1.026)	8171	0.9	3.5	93.3
Undiscounted cost and LYs	112,369	108,428	3941 (−614, 7922)	17.466	16.680	0.785 (−0.093, 1.555)	5018	3.0	2.2	93.3
MI and stroke taken into account	90,687	86,239	4448 (1066, 7642)	12.495*	11.949*	0.546 (−0.055, 1.074)*	8146	0.5	3.2	97.1
No effect of CABG beyond 5 y (HR=1 beyond 5y)										
Life-years instead of QALYs	93,510	87,428	6082 (3046, 9064)	12.405	12.096	0.310 (−0.047, 0.633)	19,639	0.0	3.4	87.4
Undiscounted cost and LYs	114,522	108,428	6094 (2372, 9793)	17.155	16.680	0.475 (−0.042, 1.244)	6094	0.5	3.1	93.2
MI and stroke taken into account	92,550	86,239	6311 (3535, 9163)	12.291	11.949	0.341 (0.000, 0.668)	18,486	0.0	2.4	90.1

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; LY, quality-adjusted life-year gained.

Costs, life-years are discounted at 3% per year.

Supplementary Table 9. Lifetime Cost-Effectiveness Results for Subgroups, expressed in Terms of Cost per Life Year gained (instead of QALY)

	Cost, $			LYs			ICER ($/LY)	% Dominant	% Dominated	%<$50K
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)				
Male (n=1377)	89,677	86,246	3431 (−1, 7248)	12.436	12.349	0.088 (−0.410, −1.308)	39,084	0.8	25.8	64.0
Female (n=389)	103,773	91,825	11,948 (3470, 17916)	12.668	11.285	1.383 (0.323, 2.048)	8639	0.1	0.6	98.7
Age ≤60 (n=553)	105,305	101,926	3378 (−3261, 9692)	16.830	16.414	0.416 (−0.436, 1.136)	8122	7.8	8.6	76.3
Age 61-70 (n=586)	92,881	88,303	4578 (−1070, 10581)	12.415	11.995	0.420 (−0.464, 1.180)	10,901	3.6	12.8	74.0
Age >70 (n=627)	80,810	73,555	7254 (1972, 12302)	8.711	8.365	0.346 (−0.500, 1.082)	20,953	0.2	18.2	70.5
Diabetes (n=1272)	97,787	91,943	5843 (−378, 12214)	12.202	11.402	0.801 (−0.099, 1.633)	7299	2.6	3.1	92.0
No diabetes (n=494)	90,383	85,644	4739 (908, 8519)	12.595	12.370	0.225 (−0.337, 0.746)	21,078	0.1	20.6	69.5
LM disease (n=694)	93,732	86,114	7618 (2225, 12734)	11.895	12.119	−0.225 (−1.027, 0.566)	PCI Dominant	0.0	72.5	15.5
3-vessel disease, no LM (n=1072)	91,619	88,270	3350 (−673, 7368)	12.891	12.080	0.811 (0.234, 1.327)	4129	5.2	0.1	94.5
SYNTAX Score ≤22 (n=562)	95,624	92,582	3043 (−2826, 9205)	13.019	13.176	−0.157 (−1.009, 0.616)	PCI Dominant	1.8	51.7	25.8
SYNTAX Score 23-32 (n=600)	87,747	83,540	4207 (−1432, 9544)	12.132	12.003	0.130 (−0.689, 0.876)	32,487	1.9	32.9	54.1
SYNTAX Score ≥33 (n=595)	94,309	86,384	7925 (2740, 13296)	12.364	11.156	1.208 (0.500, 1.923)	6560	0.2	0	99.7
US patients (n=241)	105,396	96,015	9382 (−1623, 20402)	12.999	12.026	0.973 (−0.262, 2.109)	9641	3.2	3.9	88.9
Non-US patients (n=1525)	90,500	86,086	4414 (1027, 7601)	12.435	12.107	0.328 (−0,170, 0.801)	13,445	0.2	8.9	88.4

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; LY, life-year gained. Costs and LYs are discounted at 3% per year.

Supplementary Table 10. Sensitivity Analysis on Stent Price in Overall Population and SYNTAX Score

Population	Base case with stent price of $1500	Required stent price at which the ICER of CABG vs. PCI equals $50,000/QALY gained	Interpretation of sensitivity analysis (other things equal)
Overall (n=1766)	CABG economically attractive	$ −775	Stent price does not influence economic attractiveness
SYNTAX Score ≤22 (n=562)	PCI dominant	$ 4880	Stent price above this threshold will make PCI economically unattractive
SYNTAX Score 23-32 (n=600)	CABG economically attractive	$ 1195	Stent price below this threshold would make PCI economically attractive
SYNTAX Score ≥33 (n=595)	CABG economically attractive	$ −7850	Stent price does not influence economic attractiveness

Supplementary Table 11. Cost-Effectiveness Results incorporating Productivity Losses

	Cost, $			QALYs			ICER ($/QALY)	% CABG Dominant	% CABG Dominated	%CABG <$50K*
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)				
Base case lifetime analysis	95,744	89,706	6037 (2703, 9108)	10.544	10.237	0.307 (−0.105, 0.678)	19,650	0.0	6.5	81.5
LM disease (n=694)	97,026	88,423	8602 (3105, 13690)	9.94	10.233	−0.29 (−1.00, 0.37)	PCI dominant	0.0	82.3	7.5
3-vessel disease (n=1072)	94,817	90,528	4288 (214, 8211)	10.92	10.24	0.68 (0.17, 1.10)	6280	2.1	0.2	99.3
SYNTAX Score ≤22 (n=562)	98,918	94,846	4072 (−1920, 10201)	10.97	11.17	−0.20 (−0.95, 0.46)	PCI dominant	0.8	65.8	18.8
SYNTAX Score 23-32 (n=600)	90,988	85,764	5224 (−453, 10662)	10.29	10.18	0.114(−0.60, 0.79)	45,678	1.0	35.0	52.2
SYNTAX Score ≥33 (n=595)	97,491	88,728	8763 (3576, 14201)	10.36	9.40	0.96 (0.35, 1.58)	9088	0.1	0.2	99.5

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio for CABG vs. PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year gained; LM, left main;

* Probability that CABG is the preferred strategy at a societal ICER of $50,000/QALY gained

Costs and QALYs are discounted at 3% per year.

CHAPTER 12

A European Perspective on the Cost-Effectiveness of Percutaneous Coronary Intervention with Drug-Eluting Stents vs. Bypass Surgery for Patients with Three-Vessel or Left Main Coronary Artery Disease: Final Results from the SYNTAX Trial and Economic Application of the SYNTAX Score II

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Submitted.

ABSTRACT

Aims

Recent cost-effectiveness analyses of percutaneous coronary intervention (PCI) vs. coronary artery bypass grafting (CABG) have been limited by a short time-horizon or were restricted to the U.S. healthcare perspective. We therefore used individual patient-level data from the SYNTAX trial to evaluate the cost-effectiveness of PCI vs. CABG from a European (Dutch) perspective.

Methods and Results

Between 2005 and 2007, 1800 patients with three-vessel or left main CAD were randomized to either CABG (n = 897) or PCI with DES (n = 903). Costs were estimated for all patients based on observed healthcare resource utilization over 5 years of follow-up. Health state utilities were evaluated with the EuroQOL questionnaire. A patient-level microsimulation model based on Dutch life-tables was used to extrapolate the 5-year in-trial data to a lifetime horizon.

Although initial procedural costs were lower for CABG, total initial hospitalisation costs per patient were higher (€17506 vs. €14037, $p < 0.001$). More frequent hospitalisations, repeat revascularization procedures, and higher medication costs made PCI more costly over the next 5 years. Nevertheless, total 5 year costs remained €2465/patient higher with CABG. When the in-trial results were extrapolated to a lifetime horizon, CABG was projected to be economically attractive relative to DES-PCI, with gains in both life expectancy and quality-adjusted life expectancy. The incremental cost-effectiveness ratio (€5390/QALY gained) was favourable and remained <€80000/QALY in >90% of the bootstrap replicates. Outcomes were similar when incorporating the prognostic impact of non-fatal MI and stroke, as well as across a broad range of assumptions regarding the effect of CABG on post-trial survival and costs. However, DES-PCI was economically dominant compared with CABG in patients with a SYNTAX Score ≤22 or in those with left main disease. In patients for whom the SYNTAX Score II favoured PCI based on lower predicted 4 year mortality, PCI was also economically dominant, whereas in those patients for whom the SYNTAX Score II favoured surgery, CABG was highly economically attractive (ICER range, €2967 to €3737/QALY gained).

Conclusions

For the broad population with three-vessel or left main disease who are candidates for either CABG or PCI, we found that CABG is a clinically and economically attractive revascularization strategy compared with DES-PCI from a Dutch healthcare perspective. The cost-effectiveness of CABG vs. PCI differed according to several anatomic factors, however. The newly developed SYNTAX Score II provides enhanced prognostic discrimination in this population and may be a useful tool to guide resource allocation as well.

INTRODUCTION

Approximately 2% of the total healthcare expenditure in the European Union is spent on the treatment of coronary artery disease (CAD).[1] Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for multivessel CAD have been compared in several studies. For patients without diabetes mellitus, these studies have demonstrated similar short- and long-term survival with either procedure, but CABG provided better angina relief and led to less frequent repeat revascularisation procedures.[2-8] Long-term economic evaluations have found that while PCI is cost-saving in the short term, CABG is an economically attractive treatment option compared with balloon angioplasty or PCI using bare metal stents.[9]

The Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial is the largest trial to date to compare PCI with CABG in a broad patient population. In contrast to earlier studies, the SYNTAX trial recruited patients with complex CAD (three-vessel or left main disease), used drug-eluting stents (DES), and applied an all-comers design, with minimal exclusion criteria. At 5-year follow-up, CABG had a lower rate of the composite endpoint of all-cause death, myocardial infarction, stroke or repeat revascularisation compared with DES-PCI-- driven mainly by lower rates of non-fatal myocardial infarction (MI) and repeat revascularisation with CABG. Based on the SYNTAX trial data, the SYNTAX Score II was recently developed and validated as a tool for weighing anatomical and clinical factors to establish the optimal revascularisation strategy for individual patients with complex CAD.[10, 11]

Since healthcare spending outpaces the growth of the overall economy in virtually all Western countries, long-term clinical outcomes and lifetime cost-effectiveness analyses of the two alternative revascularisation strategies are crucial for clinical guideline development and healthcare policy. Although the U.S. and European healthcare systems differ significantly with respect to clinical practice patterns, availability of resources and prices, few economic evaluations of CABG vs. PCI have been performed from a European perspective.[7, 12] Moreover, the available European economic substudies are >10 years old and have incorporated only a brief time horizon. We therefore performed a prospective health economic study alongside the SYNTAX trial, adopting a Dutch perspective and disease-simulation techniques to extrapolate the 5-year trial results to a lifetime horizon. In addition, we analysed the economic outcomes in subgroups defined on the basis of the new SYNTAX Score II,[10] hypothesizing that this tool would be a good discriminator of economic outcomes and healthcare value.

METHODS

Trial Design

The design and methods of the SYNTAX trial have been described previously.[13-15] A heart team, consisting of a cardiac surgeon and interventional cardiologist screened consecutive patients with *de novo* three-vessel or left main (isolated or associated with 1, 2 or 3-vessel disease) CAD. Between March 2005 and April 2007, 1800 patients who were considered by the Heart Team to be equally suitable for revascularisation using DES-PCI or CABG, were randomized. Patients were enrolled in 85 centres in 17 European countries and the United States. CABG was performed using standard techniques, and PCI procedures utilised paclitaxel-eluting stents (TAXUS Express, Boston Scientific, Natick, MA, USA). The institutional review board at each participating site approved the protocol, and all patients provided written informed consent. The trial complies with the Declaration of Helsinki and is registered at the National Institutes of Health website (http://www.clinicaltrials.gov; identifier NCT00114972).

Clinical Outcomes, Resource Utilisation and Medical Cost Estimation

Research coordinators at each site collected patient characteristics, procedural details, resource utilisation and clinical outcomes during the initial hospitalisation and 5-year follow-up period. A blinded clinical events committee reviewed all components of the primary clinical endpoint (death, MI, stroke, repeat revascularisation), while other clinical outcomes and measures of resource utilisation (e.g. length of stay) were collected on-site and were independently monitored.

Costs for the index hospitalisation and the five-year follow-up period were assessed by combining resource-based and event-based methods as described below. All costs were assessed from the perspective of the Dutch healthcare system and are reported in Euros. The Dutch Manual for Cost-analysis in Healthcare was utilised,[16] and where necessary the consumer price index was used to convert costs to the year 2012.[17] As recommended by the Dutch Council for Public Health, a willingness-to-pay (WTP) threshold level of €80 000/QALY was used to assess cost effectiveness.[18]

Procedural Costs

Detailed resource use was recorded for each revascularisation procedure, and the cost for each item was estimated using hospital acquisition costs at the Erasmus Medical Center, Rotterdam, the Netherlands. The cost of DES and bare metal stents were €935 and €738, respectively. Costs of antithrombotic therapy were based on acquisition costs for Dutch pharmacies.[19] Costs for non-physician personnel, disposables, perfusion (CABG), overhead and depreciation of the cardiac catheterization laboratory and the operating

room were estimated using a detailed micro-costing approach at the Erasmus Medical Centre. Costs for each procedure were adjusted for procedure duration. Initial and planned staged PCI procedures were combined in the calculation of the index resource utilisation and procedure cost.

Post-Procedure Hospitalisation Costs

All other hospitalisation costs associated with coronary revascularisation were estimated using costs for hospital stay (€2198 and €485 per night for intensive care and normal ward stay, respectively). These costs were based on multiple Dutch micro-costing studies and incorporate nursing, nutrition, materials, equipment, overhead and housing.[16] In order to apply the same costs to other countries with different practice patterns, we used regression models to adjust length of stay after PCI or CABG to Dutch norms. Separate linear regression models for PCI and CABG were developed; for each model, total length of stay was the dependent variable and independent variables included socio-demographic factors, comorbidities, in-hospital complications, and the enrolling country. Details of the models are provided in the Appendix, Supplementary Table 1.

For follow-up cardiovascular hospitalisations that did not involve a revascularisation procedure, the hospital admission was assigned to the appropriate diagnosis-related group (DRG) based on the principal diagnosis and any procedures performed during that admission. Costs were assigned based on the mean reimbursement rate for that DRG across three Dutch hospitals.

Physician Costs

Physician fees for PCI and CABG procedures were based on honoraria for these procedures set by the Dutch National Health Tariffs Authority.[16] Non-procedure related physician fees were assigned based on a fixed proportion of the costs per night in the intensive care ward.[16] Physician fees for all other hospitalisations were DRG-based and calculated as the mean honorarium across three Dutch hospitals.

Outpatient Costs

Costs for outpatient visits, tests and procedures were based on tariffs set by the Dutch National Health Tariffs Authority, and the Dutch Manual for Cost-analysis in Healthcare.[16] Medication costs were based on the acquisition costs for Dutch pharmacies.[19]

Quality of Life

Quality of life was assessed directly from patients at baseline, 1, 6, 12, 36, and 60 months using the EuroQOL (EQ-5D) health status instrument and converted to utility weights (range 0-1) using an algorithm developed for the Dutch population.[20]

Statistical Analysis

To account for the higher rate of withdrawal prior to treatment among patients assigned to CABG, we used the modified intention-to-treat (mITT) population as the primary population for the economic analysis. This mITT population was defined as all 1766 randomized patients who underwent ≥1 initial revascularisation procedure, with patients categorized according to their assigned treatment. A secondary analysis used the per protocol (PP) population and included only those patients who underwent the assigned revascularisation procedure (n = 1739).

Categorical data are reported as frequencies, and continuous data are reported as mean ± standard deviation. Discrete variables were compared using Fisher exact tests. Normally distributed continuous variables were compared using Student *t*-tests, and non-normally distributed data were compared using the Wilcoxon rank-sum test. Treatment effects from Poisson regression models were used for the comparison of hospitalisation rates. Kaplan-Meier survival curves and log-rank tests were used for the comparison of five-year clinical events. Cost data are reported as both mean and median values and were compared using *t*-tests, which are appropriate given our focus on comparing mean costs between groups (rather than the underlying distributions).[21] Confidence intervals for the differences in costs between treatment groups were obtained via bootstrapping.[22]

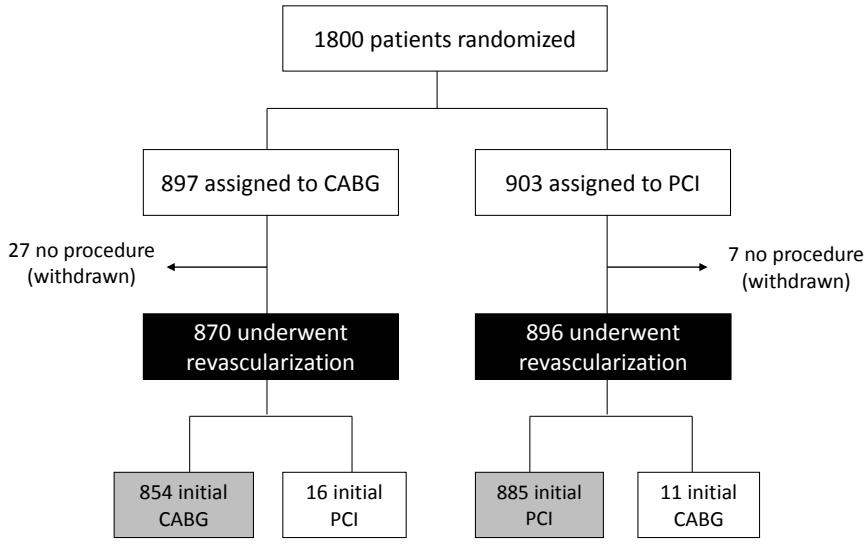

Figure 1.
CONSORT diagram. Black boxes represent the modified intention-to-treat (mITT) population that was the primary analytic population for the economic study. The grey boxes represent the per protocol (PP) population. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Quality-adjusted life expectancy was calculated for each patient as the time-weighted average of his/her utility values, using the mid-point between assessments as the transition between health states, starting at the 30-day visit. The baseline utility was applied to the time from randomization to the index procedure, and the 30-day utility value was applied to the period from the procedure through the midpoint between the 30-day and 6-month follow-up. Missing utility values were estimated using multiple imputation, taking into account baseline patient characteristics, antecedent clinical events, previous utility values and number of hospitalisations.

In-Trial Analysis of Costs, Life Years and Quality-Adjusted Life Years

To accommodate differential follow-up duration, methods for the analysis of censored data were used to obtain estimates of cumulative costs and quality-adjusted life-years gained (QALY) over time. An inverse probability-weighted estimator was applied, whereby the time axis was divided into 3-month intervals, and costs for each interval were estimated as the observed costs during the interval for patients with complete data divided by the probability of not being censored within the interval.[23] Similar methods were applied to estimate quality-adjusted life expectancy. Life-years gained at annual time points were estimated as the difference in the area between the Kaplan-Meier survival curves for the two treatment groups. The confidence limits for the mean cumulative cost, life-year, and QALY estimates for each treatment group, as well as the difference between groups were calculated using the bootstrap method.[22]

Cost-Effectiveness

The cost-effectiveness of CABG vs. PCI was assessed over a life-time horizon. Health benefits were expressed in QALYs gained in the primary analysis and as life-years gained in secondary analyses.[16, 24] Life-years and QALYs were discounted at 1.5% annually, and costs at 4% annually, as recommended by the Dutch Manual for Cost-analysis in Healthcare.[22] The analyses were based on a combination of (1) observed in-trial cost and quality of life data and (2) projections of post-trial costs, life expectancy and quality-adjusted life expectancy obtained from a Markov disease-simulation model. In this model, each surviving patient was assumed to encounter a monthly risk of death, based on age-, and sex-matched risk of death obtained from Dutch life tables, which were calibrated to the observed five-year mortality for the trial population.[25, 26]

For the PCI group, the comparison of the observed five-year mortality for the trial population with that of an age-, and sex-matched Dutch population, yielded a multiplier of 1.30. To incorporate the prognostic benefit of CABG vs. PCI, an additional multiplicative factor was applied, based on the hazard ratio (HR) derived from an analysis of all-cause mortality from the SYNTAX patients. In sensitivity analyses, the independent impact of non-fatal

events (myocardial infarction [MI] and stroke) on long-term mortality was taken into account. For these secondary analyses, events were used as time-varying covariates and analyses were adjusted for baseline characteristics (age, sex and diabetes) and treatment group. The resulting mortality HRs were used as multipliers for patients with a non-fatal MI and non-fatal stroke. Patient-level costs and utility weights for each projected year of life beyond the trial observation period were derived from regression models developed from the in-trial data (Appendix, Supplementary Tables 3 and 4).

Three sets of analyses were performed based on different assumptions regarding the duration of the prognostic benefit of CABG compared with PCI. The base case analysis assumed that the benefit of CABG tapered in a linear fashion from years 5 to 10 and that there were no prognostic differences between PCI and CABG beyond year 10 (i.e. HR=1 after year 10). In sensitivity analyses, we assumed (1) a constant prognostic benefit of CABG from year 5 to year 10, with no benefit of CABG after 10 years; or (2) no prognostic benefit of CABG beyond the 5-year trial period (i.e. HR=1 after year 5).

In addition to the overall analysis and sensitivity analyses, subgroup analyses were performed to examine the cost-effectiveness of CABG vs. DES in prespecified patient subsets stratified according to age (≤60, 61-70, >70), diabetes, left main or 3-vessel disease, and the anatomic SYNTAX score. Finally, we used the recently developed SYNTAX score II that incorporates both anatomic and clinical factors to calculate a predicted 4-year mortality for patients with CAD when treated with either DES-PCI or CABG.[10] To use this as a stratification factor, patients were assigned to 5 different categories according to the predicted difference in 4-year survival with DES-PCI vs. CABG.

Bootstrap methodology (1000 repetitions) was used to estimate uncertainty in the joint distribution of lifetime cost, life-years, and QALYs for each treatment group. To maintain consistency of the within-trial and post-trial CABG effect within each bootstrap sample, the HRs for the effect of CABG vs. PCI on mortality were re-estimated for each bootstrap replicate. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Patient Population

In SYNTAX, 1800 patients with de novo three-vessel or left main CAD were randomized to either CABG (n = 897) or PCI (n = 903). Of the randomized patients, 27 assigned to CABG and 7 assigned to PCI did not undergo any revascularisation procedure and were excluded from the primary mITT population (Figure 1). There were no significant differences

Table 1. Baseline Characteristics (mITT Population)

	CABG (n=870)	PCI (n=896)	*p*-value
Sociodemographic characteristics			
Age, y	64.9 ± 9.8	65.3 ± 9.6	0.40
Male, %	79.4	76.6	0.15
Body mass index, kg/m^2	27.9 ± 4.4	28.1 ± 4.8	0.26
Enrolled in the Netherlands, %	8.5	8.3	0.85
Clinical characteristics			
Diabetes mellitus, %	27.6	28.3	0.72
Insulin-dependent, %	10.1	9.9	0.90
Current smoker, %	22.0	18.5	0.07
Previous MI, %	33.3	32.1	0.59
Peripheral vascular disease	10.5	9.2	0.36
COPD, %	9.2	7.9	0.34
Prior stroke or TIA, %	9.1	7.7	0.29
History of CHF, %	5.2	4.0	0.27
Angiographic characteristics			
LVEF, %	58.3 ± 13.2	59.1 ± 12.9	0.31
LM disease (any), %	39.4	39.3	0.98
LM only	5.4	4.5	0.98
1 other artery	8.1	7.5	0.36
2 other arteries	12.2	12.4	0.65
3 other arteries	13.7	15.0	0.90
Three-vessel disease (no LM), %	60.6	60.7	0.98
SYNTAX Score	29.1 ± 11.3	28.4 ± 11.4	0.21

mITT indicates modified intention to treat; CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LM, left main; LVEF, left ventricular ejection fraction; MI, myocardial infarction; mITT, modified intention-to-treat; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

in any observed baseline characteristics between the CABG and PCI groups for the mITT population (Table 1). Of the mITT patients, 148 (8.4%) were enrolled in the Netherlands, 39% had left main CAD, and the median follow-up was 60 months.

Initial Treatment Costs

Of the patients that were randomized to PCI, 885 (98.8%) underwent PCI and 11 (1.2%) underwent CABG. Among patients assigned to CABG, 854 (98.2%) underwent CABG, and 16 (1.8%) underwent PCI. Resource utilisation for the initial revascularisation procedures is summarised in Table 2 (PP population). In the PCI group, 13.6% underwent staged procedures. On average, 2.1 guiding catheters, 3.5 guidewires, 3.7 angioplasty balloons, and 4.5 drug-eluting stents were used during the initial PCI procedure. Although procedure

Table 2. Index Procedural Resource Utilisation and Cost (Per Protocol Population)

	CABG (n=854)	PCI (n=885)	*p*-value
Number of PCI procedures, %			
1	-	85.9 (760/885)	
2	-	13.5 (124/885)	
3 or more	-	0.1 (1/885)	
Procedure duration, minutes	209±62 [205]	101±55 [90]	<0.001
Guiding catheters	-	2.1 ± 1.2	
Guidewires	-	3.5 ± 2.3	
Paclitaxel-eluting stents	-	4.5 ± 2.3	
Bare metal stents	-	0.0 ± 0.3	
Angioplasty balloons	-	3.7 ± 2.8	
Rotablator burrs	-	0.1 ± 0.3	
IVUS catheters	-	0.1 ± 0.4	
Closure device	-	0.4 ± 0.6	
Contrast volume, ml	-	415 ± 207.5 [380]	
Antithrombotic agents used, %			
Bivalrudin	-	7.2% (64/885)	
Abciximab	-	15.6% (138/885)	
Eptifibatide	-	9.5% (84/885)	
Tirofiban	-	10.7% (95/885)	
Index procedure cost, €	6472 ± 1500 [6359]	7823 ± 4324 [7330]	<0.001

Values in brackets represent medians. CABG, coronary artery bypass grafting; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention.

duration was longer for CABG, initial procedure costs were ~€1351 lower with CABG as compared with PCI (€6472 vs. €7823, $p < 0.001$), owing to higher costs associated with disposable resources in the PCI group. For the mITT population, the difference in initial procedural costs was similar (€1354; €6444 vs. €7798, $p < 0.001$).

Clinical events, resource utilisation, and costs during the initial hospitalisation are summarized in Table 3. Post-procedural hospital costs were higher for the CABG group compared with the PCI group (€8725 vs. €3996, $p < 0.001$), as were physician fees (€2264 vs. €2111, $p < 0.001$). As a result, total initial hospitalisation costs were ~€3500/patient higher in the CABG group compared with the PCI group (€17506 vs. €14037, $p < 0.001$).

Follow-up Resource Utilisation and Costs

Follow-up clinical outcomes, resource utilisation, and costs are summarised in Table 4. During each year of follow-up, the annual rates of diagnostic catheterisation, repeat revascularisation, hospitalisation, and their associated costs were higher for patients

Table 3. Index Hospitalisation Events, Resource Utilisation, and Costs (mITT Population)

	CABG (n=870)	PCI (n=896)	Difference (95% CI)	*p*-value
Death, %	1.4 (12/870)	1.8 (16/896)	−0.4 (−1.6, 0.8)	0.49
MI, %	2.4 (21/870)	2.7 (24/896)	−0.3 (−1.7, 1.2)	0.72
Stroke, %	1.0 (9/870)	0.1 (1/896)	0.9 (0.2, 1.6)	0.01
Unplanned CABG, %	1.1 (10/870)	0.8 (7/896)	0.4 (−0.5, 1.3)	0.42
Unplanned PCI, %	0.5 (4/870)	1.8 (16/896)	−1.3 (−2.3, −0.3)	0.008
Complications, %				
Major bleeding	4.8 (42/870)	4.5 (40/896)	0.4 (−1.6, 2.3)	0.72
Respiratory failure	1.6 (14/870)	0.0 (0/896)	1.6 (0.8, 2.4)	< 0.001
Renal failure	2.4 (21/870)	0.7 (6/896)	1.7 (0.6, 2.9)	0.003
Wound infection	4.1 (36/870)	0 (0/896)	4.1 (2.8, 5.5)	< 0.001
Other infection	6.2 (54/870)	0.4 (4/896)	5.8 (4.1, 7.4)	< 0.001
Atrial fibrillation	17.9 (156/870)	1.3 (12/896)	16.6 (13.9, 19.2)	< 0.001
Cardiac tamponade	0.8 (7/870)	0.3 (3/896)	0.5 (−0.2, 1.2)	0.22
Other procedures, %				
Permanent pacemaker	0.6 (5/870)	0.2 (2/896)	0.4 (−0.2, 0.9)	0.28
ICD implantation	0.2 (2/870)	0.0 (0/896)	0.2 (−0.1, 0.5)	0.24
Carotid endarterectomy	0.5 (4/870)	0.0 (0/896)	0.5 (0.0, 0.9)	0.06
Length of stay*				
ICU/CCU	3.0 ± 5.2 (870)	1.6 ± 2.9 (896)	1.5 (1.1, 1.9)	< 0.001
Total	13.9 ± 10.1 (870)	6.7 ± 7.7 (896)	7.2 (6.4, 8.0)	< 0.001
Initial hospitalisation costs, €				
Revascularization procedures	6517 ± 1691 [6347]	7930 ± 4404 [7374]	−1413 (−1726, −1100)	< 0.001
Hospital stay + ancillary services	8725 ± 4818 [7117]	3996 ± 3816 [2143]	4729 (4324, 5134)	< 0.001
Physician fees	2264 ± 370 [2126]	2111 ± 587 [1887]	153 (107, 199)	< 0.001
Total	17506 ± 5621 [16214]	14037 ± 6850 [12597]	3469 (2883, 4054)	< 0.001

Values in brackets are medians. CCU, cardiac care unit; CI, confidence interval; ICD, implantable cardioverter-defibrillator; ICU, intensive care unit; mITT, modified intention-to-treat. * Length of stay in the different countries was converted to the Dutch perspective using a regression modeling approach (Supplementary Table 1).

assigned to initial PCI. In addition, costs for outpatient services and medications were consistently higher in the PCI group compared to the CABG group. Rehabilitation costs were greater in the first year after CABG and were similar between treatments in the subsequent years. Overall, the difference in cumulative medical care costs between the CABG and PCI narrowed from €3469 after the index hospitalisation to €2465 after 5 years of follow-up (Table 5 and Figure 2).

Table 4. Follow-Up Events, Resource Utilisation, and Costs (mITT Population)

	Year 1		Year 2		Year 3		Year 4		Year 5		5-year Cumulative		
	CABG n=870	PCI N=896	CABG n=813	PCI N=851	CABG n=791	PCI N=832	CABG n=767	PCI N=805	CABG n=733	PCI N=771	CABG n=870	PCI N=896	*p*-value
Clinical outcomes													
Death, %	1.8	2.6	1.5	2.0	1.9	2.6	2.2	3.2	2.9	2.3	10.7	13.6	0.06
MI, %	0.9	2.2	0.1	1.2	0.3	1.2	0.3	1.7	0.0	1.2	3.7	9.3	<0.001
Stroke, %	1.0	0.6	0.7	0.7	0.5	0.6	0.4	0.2	0.0	0.1	3.4	2.2	0.12
Resource use (events/100 pts)													
Repeat revascularisation (any)	4.8	14.1	3.9	6.6	2.5	3.7	2.2	5.5	2.6	4.3	16.6	35.2	<0.001
PCI procedures	4.7	11.9	3.9	5.6	2.5	2.8	2.2	4.8	2.6	3.1	15.3	28.9	<0.001
CABG procedures	0.1	2.1	0.0	0.9	0.0	1.0	0.0	0.6	0.0	1.2	1.3	6.3	<0.001
Diagnostic catheterization	3.8	11.6	2.3	6.5	1.9	4.1	0.1	0.2	1.4	3.4	10.1	22.3	<0.001
Re-hospitalization	27.7	41.1	16.6	20.9	12.9	15.6	14.5	18.3	11.5	13.5	77.5	103.6	<0.001
Cost per patient, €													
Rehospitalisations	1610	2647	1047	1285	919	1033	874	1092	1010	1066	-	-	-
Outpatient services	208	240	60	141	49	73	80	91	51	81	-	-	-
Rehab/skilled nursing stays	1208	114	13	13	14	13	14	15	15	16	-	-	-
Medications	132	176	152	197	156	202	159	213	167	223	-	-	-
MD fees	149	280	94	135	77	106	69	118	71	99	-	-	-
Total	3307	3457	1366	1771	1215	1427	1196	1529	1314	1485	-	-	-

CABG, coronary artery bypass grafting; MI, myocardial infarction; MD, medical doctor; mITT, modified intention-to-treat; PCI, percutaneous coronary intervention

Table 5. Cumulative In-Trial Costs, QALYs, and Life-Years, Adjusted for Censoring

Time Since Randomization	Cumulative Costs, €			Cumulative QALYs			Cumulative Life-Years		
	CABG	PCI	Δ	CABG	PCI	Δ	CABG	PCI	Δ
1 year	20868	17495	3373	0.762	0.791	−0.029	0.975	0.965	0.009
2 years	22193	19156	3037	1.547	1.600	−0.022	1.933	1.912	0.022
3 years	23364	20507	2857	2.323	2.329	−0.005	2.877	2.832	0.045
4 years	24454	21879	2575	3.074	3.058	0.016	3.800	3.732	0.069
5 years	25680	23215	2465	3.802	3.762	0.040	4.701	4.601	0.100

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-years gained. Δ=difference between CABG and PCI group; D, difference between CABG and PCI groups

Utility Weights and QALYs

For both treatment groups, utility weights improved substantially over the course of the trial (Supplementary Table 2). At 1 month follow-up, utility weights were significantly lower after CABG than PCI (0.74 vs. 0.83, $p < 0.001$), reflecting longer recovery after CABG. However, this early utility benefit of PCI was no longer significant at 6 months and longer follow-up. As a result of the early utility benefit of PCI, cumulative quality-adjusted life-years were higher with PCI than with CABG through 3 years of follow-up (Table 5). At 5

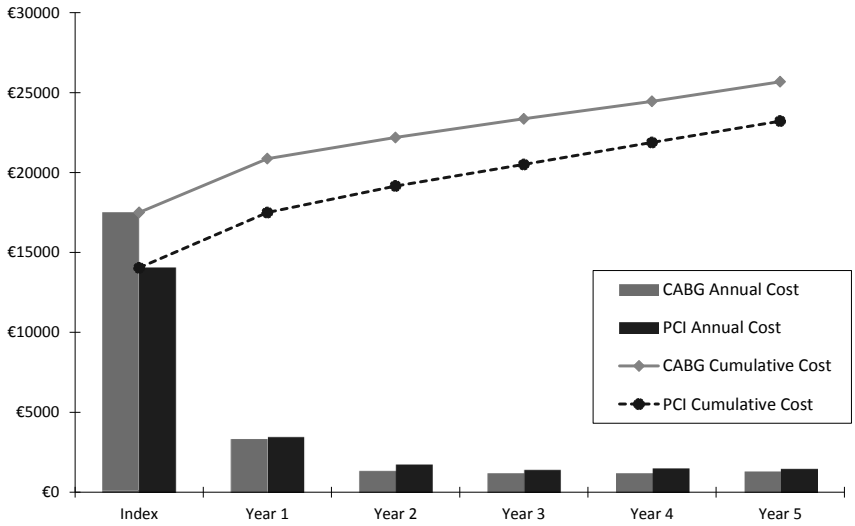

Figure 2.
Mean cumulative medical costs (lines) and mean annual follow-up costs (bars) in 2012 euros, for the PCI and CABG groups. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. Note that the first set of bars represent represents the costs of the index hospitalisation.

years, however, life expectancy (4.70 vs. 4.60 years) and quality-adjusted life expectancy (3.80 vs. 3.76 QALYs) were both greater with CABG than with PCI.

Lifetime Cost-Effectiveness - Overall Population

Results from lifetime cost-effectiveness analyses are shown in Table 6. Despite reductions in annual follow-up costs over the first 5 years of follow-up, patients in the CABG group were projected to incur €1929 higher overall healthcare costs over a lifetime horizon. Although CABG was only associated with a small gain in life expectancy (0.100 life-years) and quality-adjusted life expectancy (0.040 QALY) over the first 5 years of follow-up, extrapolation of the observed benefits over a lifetime horizon resulted in an increase in life expectancy of 0.488 years and an increase in quality-adjusted life expectancy of 0.358 QALYs with CABG as compared with PCI.

The resulting incremental cost-effectiveness ratio (ICER) for CABG vs. PCI was €5390/QALY gained, with 92.8% of bootstrap replicates falling below a societal willingness-to-pay threshold of €80000/QALY (Figures 4 and 5, and Table 6/row 1). When outcomes were expressed in life-years, CABG was associated an ICER of €3953/life-year gained (Table 6/row 2). In the analysis accounting for the prognostic impact of non-fatal MI and stroke, the benefit of CABG increased moderately to 0.399 QALYs, and the ICER was €5092/QALY

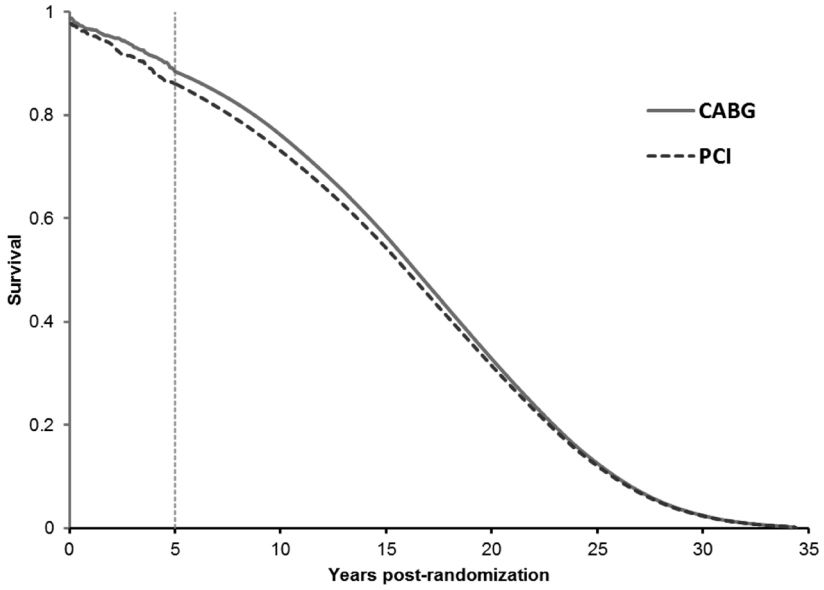

Figure 3.
Observed survival through 5 years and predicted survival beyond 5 years for the CABG and PCI groups, according to the base case assumptions. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Table 6. Lifetime Cost-Effectiveness Results for Base Case and Sensitivity Analyses

	Cost, €			QALYs			ICER (€/QALY)	% Dominant	% Dominated	%CABG <€80K*
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)				
Tapered CABG effect between 5 and 10 years										
Base case lifetime analysis	38164	36235	1929 (252, 3591)	11.782	11.424	0.358 (−0.103, 0.783)	5390	1.3	5.1	92.8
Life-years instead of QALYs*	38164	36235	1929 (252, 3591)	14.359*	13.871*	0.488 (−0.052, 0.971)*	3953*	1.3	3.4	96.3
Undiscounted cost and QALYs	47053	45501	1552 (−617, 3655)	13.975	13.517	0.458 (0.098, 0.970)	3391	7.3	4.0	94.4
Incorporate prognostic effect of MI and Stroke	37827	35796	2031 (357, 3499)	11.677	11.279	0.399 (−0.062, 0.800)	5092	0.8	4.6	94.2
Fixed CABG effect between 5 and 10 years										
Lifetime analysis	37823	36235	1588 (−118, 3296)	11.877	11.424	0.453 (−0.120, 0.975)	3505	3.7	4.9	94.3
Life-years instead of QALYs*	37823	36235	1588 (−118, 3296)	14.475	13.871	0.604 (−0.087, 1.208)	2629*	3.7	3.4	96.2
Undiscounted cost and QALYs	47053	45501	1552 (−1169, 3253)	13.975	13.517	0.458 (−0.126, 1.210)	3391	14.3	2.4	95.2
Incorporate prognostic effect of MI and Stroke	37492	35796	1695 (−29, 3208)	11.773	11.279	0.494 (−0.077, 0.986)	3429	2.6	4.8	94.6
No effect of CABG beyond 5 years										
Lifetime analysis	38550	36235	2315 (641, 3975)	11.686	11.424	0.263 (−0.082, 0.594)	8815	0.3	6.3	90.7
Life-years instead of QALYs*	38550	36235	2315 (641, 3975)	14.242	13.871	0.371 (−0.032, 0.746)	6240*	0.3	3.2	96.6
Undiscounted cost and QALYs	47513	45501	2012 (−44, 4088)	13.858	13.517	0.341 (−0.016, 0.931)	5900	2.7	5.4	93.4
Incorporate prognostic effect of MI and Stroke	38205	35796	2409 (779, 3854)	11.581	11.279	0.302 (−0.056, 0.624)	7971	0.8	3.2	95.3

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year gained. Costs are discounted at 4%, life-years and QALYs at 1.5% per year

*Results in this row represent life-years (instead of QALYs) and cost per life-year gained (instead of cost per QALY gained)

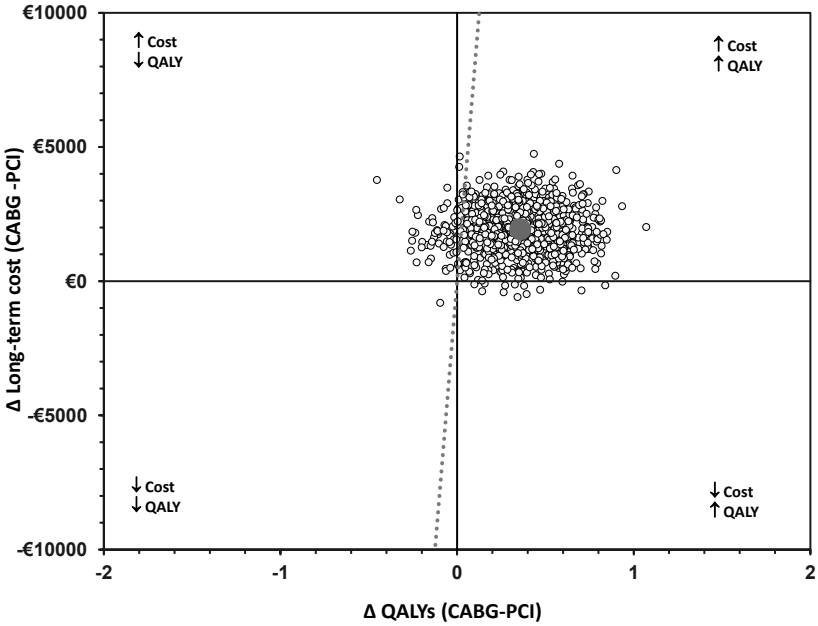

Figure 4.
Joint distribution of projected lifetime incremental costs and quality-adjusted life expectancy for CABG vs. PCI based on bootstrap replication of the SYNTAX trial population, plotted on the cost-effectiveness plane. The red circle represents the estimated mean values (incremental cost=€1929, incremental QALYs=0.358). The green line represents the €80000/QALY cost-effectiveness threshold. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year.

gained with 94.2% of bootstrap replicates below a societal willingness-to-pay threshold of €80,000 (Figure 5, Table 6/row 4).

Results were robust across a wide range of alternative assumptions regarding the duration and magnitude of the benefit of CABG over PCI on both costs and survival beyond the 5 year timeframe observed in the trial. Assuming that the benefits of CABG would remain constant from year 5 to year 10, with no further benefit beyond 10 years, the ICER for CABG vs. PCI was €3505/QALY gained. When we conservatively assumed that there would be no benefit of CABG beyond the 5-year trial period, the ICER increased to €8815/QALY gained with 90.7% of the bootstrap replicates below the €80000/QALY threshold. Results were similar when the analysis incorporated the prognostic impact of non-fatal MI and stroke, or when effectiveness was expressed in life-years rather than QALYs (Supplementary Tables 6 and 7).

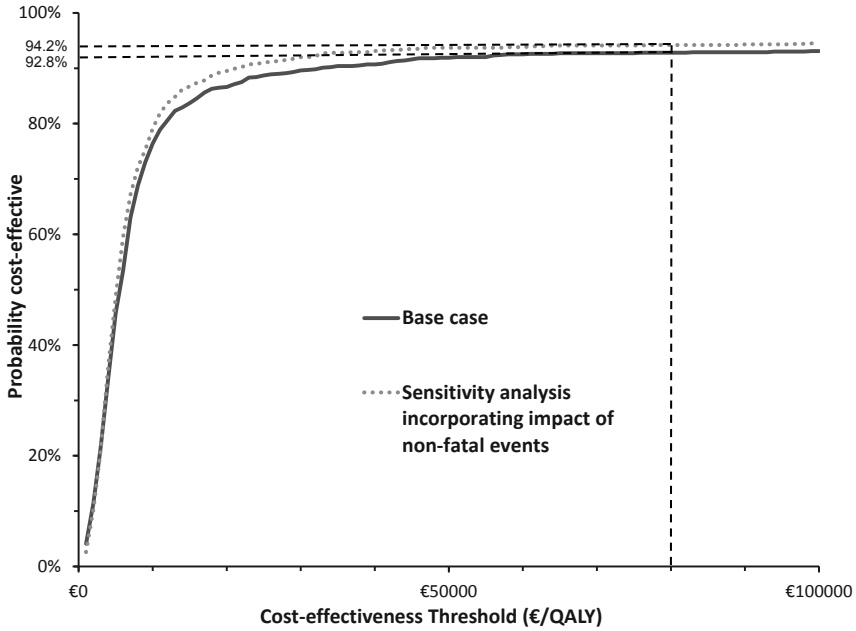

Figure 5.
Cost effectiveness acceptability curve of CABG vs. PCI. The probability that CABG is cost-effective is calculated as the proportion of bootstrap-derived estimates falling below a given cost-effectiveness threshold and is plotted across a range of possible cost-effectiveness thresholds. The solid blue line represents the base-case analysis, while the dashed red line indicates the analysis in which the impact of MI and stroke were taken into account.

Subgroup Analyses and the Impact of Stent Pricing

Results from the pre-specified subgroup analyses are summarised in Table 7. For most subgroups, the results were similar to those of the overall trial population albeit with greater uncertainty due to the reduced sample sizes. However, the results in 4 subgroups differed substantially from those of the overall trial. For patients with less complex coronary anatomy (SYNTAX Score ≤22), PCI was projected to increase quality-adjusted life expectancy and to reduce costs compared with CABG. For this subgroup, CABG was only economically attractive in 28.7% of the bootstrap replicates at an ICER of €80000/QALY. Conversely, for patients with SYNTAX Scores of 23-32 and ≥33, the ICERs for CABG vs. PCI were €54475/QALY gained and €1787/QALY gained, respectively.

PCI was an economically dominant strategy for patients with left main CAD, whereas CABG was highly economically attractive compared with PCI for patients with three-vessel disease (ICER €1174/QALY gained). For all other subgroups, CABG was economically attractive compared with PCI with ICERs <€20,000/QALY gained. Importantly, results for the population of patients enrolled in the Netherlands (n = 148) were consistent with

Table 7. Lifetime Cost-Effectiveness Results for Subgroups

	Cost, €			QALYs			ICER (€/QALY)	% CABG Dominant	% CABG Dominated	%CABG <€80K*
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)				
Age ≤60 (n=553)	39860	39162	697 (−2304, 4041)	16.864	16.560	0.303 (−0.411, 1.108)	2298	26.7	8.9	84.7
Age 61-70 (n=586)	38220	36653	1567 (−1054, 4634)	11.447	11.270	0.178 (−0.459, 1.105)	8826	11.1	14.5	81.7
Age >70 (n=627)	36502	33319	3182 (424, 6125)	7.361	7.163	0.198 (−0.554, 0.900)	16085	0.7	25.3	70.0
Diabetes (n=1272)	39360	37875	1485 (−1500, 4742)	11.161	10.689	0.472 (0.164, 1.431)	3143	12.3	5.5	92.8
No diabetes (n=494)	37675	35585	2090 (−29, 3965)	11.992	11.714	0.278 (−0.344, 0.690)	7509	2.0	23.8	72.9
LM disease (n=694)	40269	37034	3235 (623, 6086)	11.025	11.471	−0.445 (−1.158, 0.359)	PCI dominant	0.1	80.8	15.6
Three-vessel disease (n=1072)	36743	35725	1018 (−1076, 2884)	12.261	11.393	0.868 (0.215, 1.271)	1174	0.0	0.1	79.2
SYNTAX Score ≤22 (n=562)	39230	37730	1500 (−1940, 4589)	12.498	12.502	−0.004 (−0.980, 0.537)	PCI dominant	6.6	51.6	28.7
SYNTAX Score 23-32 (n=600)	36431	33935	2496 (101, 5270)	11.444	11.398	0.0458 (−0.625, 0.841)	54475	0.1	34.0	61.3
SYNTAX Score ≥33 (n=595)	39017	37036	1982 (−1051, 4794)	11.480	10.371	1.109 (0.298, 1.740)	1787	10.3	0.5	99.4
Difference in 4 year predicted mortality (SYNTAX Score II)										
≥2% in favor of PCI (n=281)	36060	36359	−299 (−4950, 4572)	8.079	9.416	−1.336 (−2.531, 0.065)	PCI dominant	1.1	44.7	2.9
0-2% in favor of PCI (n=235)	37637	34227	3409 (−1359, 8185)	11.593	12.473	−0.880 (−2.788, 0.599)	PCI dominant	0.6	78.4	15.2
0-2% in favor of CABG (n=467)	34953	34425	527 (−1934, 3242)	14.014	13.873	0.141 (−0.748, 1.119)	3737	21.3	18.8	71.7
2-5% in favor of CABG (n=320)	40205	37318	2887 (−1536, 6851)	13.613	12.840	0.773 (−0.413, 1.259)	3733	7.9	10.4	86.6
≥5 in favor of CABG (n=463)	41158	38116	3041 (−240, 6969)	9.847	8.822	1.025 (0.358, 1.995)	2967	3.4	0.2	99.8
Dutch patients (n=148)	36032	34996	1036 (−6570, 7168)	12.835	11.147	1.688 (−0.274, 2.409)	614	43.6	2.4	94.7
Non-Dutch patients (n=1618)	38348	36346	2002 (294, 3694)	11.674	11.449	0.225 (−0.202, 0.715)	8898	1.2	13.0	85.2

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio for CABG vs. PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year gained; LM, left main.

* Probability that CABG is the preferred strategy at a societal ICER of €50000/QALY or 80000/QALY gained.

Costs are discounted at 4%, life-years and QALYs at 1.5% per year.

those for the overall population as well. Results for subgroups were unchanged when we considered the impact of non-fatal MI and stroke on mortality (Supplementary Table 5).

When stratified according to differences in predicted 4-year mortality based on the SYNTAX score II, we found that the tool not only discriminates well for 4-year mortality but also for long-term economic outcomes (Figure 6). For patients in whom PCI was estimated to result in better 4-year survival, PCI was also economically dominant. For patients in whom CABG was predicted to result in better 4 year survival, CABG was also highly economically attractive (ICERs ranging from €2967 to €3737 per QALY gained). In the SYNTAX Score II groups where CABG was preferred, the probability that CABG was economically dominant ranged from 71.7% to 99.8%.

We also performed a sensitivity analysis varying the acquisition cost of DES (Figure 7). Although the ICER for CABG vs. PCI increased as the acquisition cost of DES decreased, even at a DES price of €0, the ICER for CABG remained <€20,000/QALY gained in the overall population. When this analysis was repeated within strata according to SYNTAX

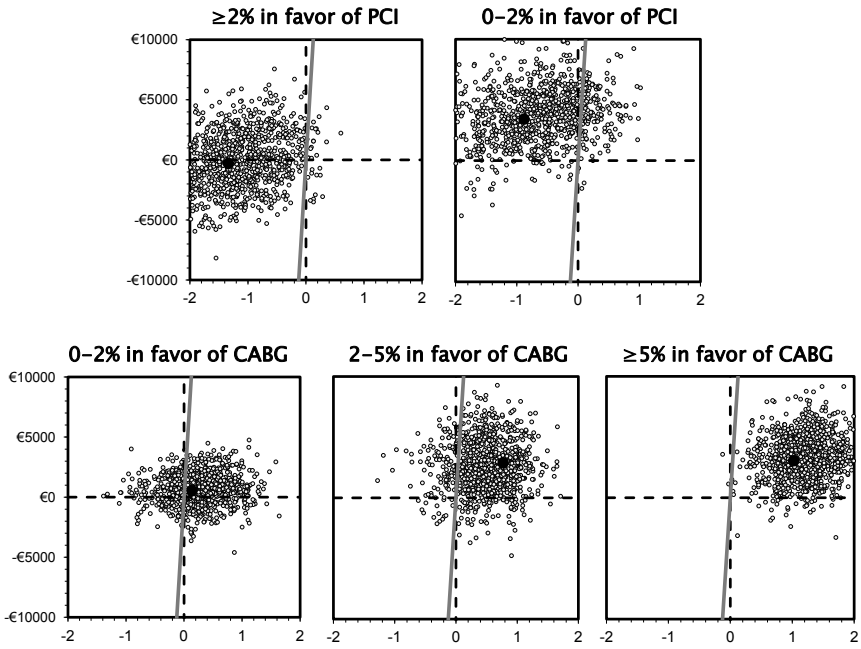

Figure 6.
Joint distribution of projected lifetime incremental costs and quality-adjusted life expectancy for CABG vs. PCI within subgroups stratified according to differences in predicted 4-year mortality based on the SYNTAX Score II. For each stratum, the red circle represents the estimated mean values. The green line represents the €80000/QALY cost-effectiveness threshold. Horizontal axes: difference in quality-adjusted life years (CABG-PCI). CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

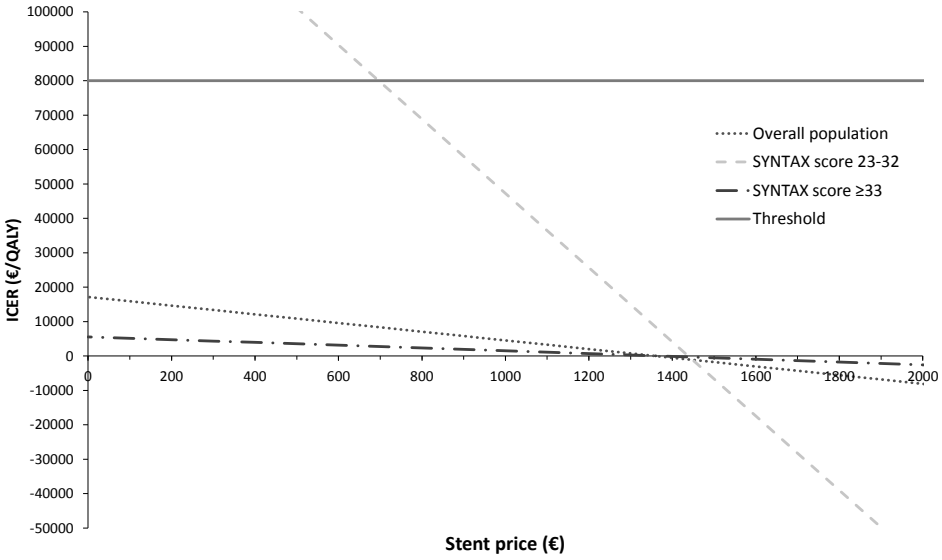

Figure 7.
Sensitivity analysis of the ICER for CABG vs. PCI as a function of the stent price in the overall population and according to the anatomic SYNTAX Score. The green line represents a cost-effectiveness threshold of €80,000/QALY. The negative ICERs for the low SYNTAX Score population indicate that PCI was economically dominant over the full range of stent prices displayed.

Score, only the intermediate SYNTAX Score tertile was sensitive to stent price (Figure 7 and Supplementary Table 7). For patients with a SYNTAX Score ≤22, the PCI strategy remained economically attractive unless the stent price exceeded €1400/stent, while for patients with a SYNTAX Score ≥33, CABG remained economically attractive at all stent acquisition costs. However, among patients with SYNTAX Scores between 23 and 32, the ICER for CABG vs. PCI remained <€80,000/QALY gained only if the DES acquisition cost was >€675/stent.

DISCUSSION

This economic substudy of the SYNTAX trial is the first to directly compare long-term clinical and economic outcomes of DES-PCI vs. CABG among patients with three-vessel or left main CAD from a Dutch healthcare perspective. Our results reveal that initial hospitalisation costs were higher with CABG, and these up-front costs were only partially offset by improved clinical outcomes and lower resource use utilisation during follow-up. Over the first 5 years of follow-up, CABG improved life expectancy and quality-adjusted life expectancy (by 0.10 years and 0.040 QALYs, respectively) while increasing costs by ~€2500 compared with DES-PCI. These in-trial life expectancy results were magnified

when extrapolated over a patient's lifetime (0.358 QALYs and 0.488 life years gained with CABG vs. DES-PCI), while the cost difference narrowed further (~€1900 higher costs with CABG vs. DES-PCI). In the base case analysis, the resulting lifetime cost-effectiveness ratios for CABG vs. DES-PCI were €5390/QALY gained and €3953/life year gained, values that are considered highly cost-effective from a Dutch perspective. These results were robust to a variety of alternative assumptions regarding the duration and magnitude of the benefit of CABG over PCI, stent pricing, and the prognostic impact of non-fatal myocardial infarction and stroke.

For most subgroups, the results were similar to those of the overall trial population albeit with more uncertainty due to the reduced sample sizes. In patients with a SYNTAX Score ≤22, however, DES-PCI was associated with a small lifetime gain of 0.004 QALY compared with CABG, resulting in an economically dominant position compared with CABG. These results suggest that for patients with relatively straightforward 3-vessel or left main CAD, DES-PCI might be the preferred revascularization strategy on both clinical and economic grounds. In contrast, in the subgroup with highly complex CAD (SYNTAX Score ≥32), CABG was strongly favoured on clinical and economic grounds (1.109 QALY gain, €1982 higher costs compared with DES-PCI). In the intermediate SYNTAX Score group, CABG was associated with a small 0.049 QALY gain, surrounded by large uncertainty. We also found that by incorporating both clinical and anatomic factors, the SYNTAX Score II can be a valuable discriminator of health care value for patients with complex CAD.

While device prices are often perceived to be an important driver of cost-effectiveness,[27] our results were not sensitive to the stent price. Indeed, the major determinant of cost-effectiveness in our DES-PCI vs. CABG comparison was the gain in (quality-adjusted) life expectancy rather than the cost difference. Therefore, we found no device cost at which DES-PCI would have been an economically attractive treatment option in the overall population, or in patients with a SYNTAX Score ≥32. Only in the intermediate SYNTAX Score group did stent price affect the ICER materially; indeed, for that subgroup, reducing the stent price by ~25% from current levels would make DES-PCI the preferred treatment option on economic grounds.

Role of the SYNTAX Score II

Our paper is the first to examine the economic implications of the SYNTAX Score II. The SYNTAX Score II was recently introduced to provide an objective, evidence-based tool to enhance individualized decision-making for patients with complex CAD.[10] This score predicts 4-year mortality with PCI or CABG and was constructed using both anatomical predictors (i.e. the anatomical SYNTAX Score) and clinical factors including age, gender, renal function, left ventricular ejection fraction, chronic obstructive pulmonary disease

and peripheral vascular disease. In this analysis, we found that selecting patients for PCI vs. CABG based on 4-year mortality projections leads to treatment decisions that are both clinically and economically attractive.

Comparison with Previous Studies

Our results are remarkably different from the cost-effectiveness of DES-PCI vs. CABG based on the 1-year SYNTAX data.[28] In that early analysis, DES-PCI was associated with a small QALY gain and ~$3600 lower costs, suggesting that DES PCI was economically dominant compared with CABG. In the current study however, quality-adjusted life expectancy was higher with CABG such that the surgical option was highly cost-effective for most patients despite higher short- and long-term costs. This discrepancy between the 1-year and lifetime cost-effectiveness of DES-PCI and CABG, emphasizes the importance of basing policy decisions on trials with long-term follow-up in order to capture benefits that emerge at later time points.

To date, few studies on the cost-effectiveness of CABG vs. PCI have been performed from a European country perspective.[9] The economic substudy of the Arterial Revascularization Therapy Study (ARTS) found that after 3-year follow-up CABG was associated with €1798 higher costs than PCI using bare metal stents, but did not use QALYs to express benefits and did not project their findings over a lifetime horizon.[29] Recently, a small (n = 199) observational study applied an Austrian healthcare perspective to assess the cost-effectiveness of CABG vs. DES-PCI. They found that CABG was associated with €5400 higher costs at 5-years, leading to an ICER of €45615 per death, myocardial infarction, stroke or repeat revascularization avoided.[30] Although results were not expressed in euros/QALY, similar to our results, the ICER (expressed in cost per event avoided) was more favourable for CABG in those subgroups with a higher SYNTAX Score.

Country-Specificity of Cost-Effectiveness Results

There are many reasons why cost-effectiveness results may vary across countries, including differences in severity of disease, epidemiological context, healthcare system characteristics, clinical practice patterns, and different prices for resources and labour. Therefore guidelines for economic evaluations strongly recommend the application of local costing methodology.[16, 31, 32] It is nonetheless instructive to compare the results of the current Dutch perspective analysis with those from the recently published US perspective analysis.[33] Although costs, EQ-5D utilities, and calibration factors for the lifetime model differed, the overall results of the 2 studies are nonetheless quite similar. In the US analysis, the base case ICER for CABG vs. DES-PCI was $16,537/QALY gained, a result that corresponds (after application of purchasing power parity conversion factors[34]) to €10569/QALY gained from a Dutch perspective. Some differences in the ICERS are to

be expected since purchasing power parities are generic conversion factors that are not tailored to highly specific analyses of any specific procedure or treatment as performed in this study.

Limitations

This study has several limitations. Although the SYNTAX trial enrolled patients from 18 countries, the current analysis was performed from a Dutch healthcare perspective. Although we were careful to assign costs at levels of resource utilization that were unlikely to differ by country, this was not possible for length of stay. We therefore used regression modeling to adjust length of stay at the individual country level to Dutch norms. Following existing recommendations for economic analyses alongside multinational trials, all clinical outcomes were assumed to be similar across countries.[35] Restricting our analysis to Dutch patients only would have severely reduced our sample size and increased uncertainty in the results. Nonetheless, it is reassuring that our results were very similar when restricted to only Dutch trial participants.

In addition, our study was limited by the need to extrapolate results from 5-years to a lifetime horizon, necessitating assumptions with respect to the impact of CABG on long-term survival, quality-of-life and healthcare costs. We used all possible data from the trial to inform these extrapolations and varied assumptions in sensitivity analyses, which produced similar results as our base case analysis. Finally, DES-PCI was performed using first generation (paclitaxel-eluting) DES. Therefore, our results may not be generalisable to settings where second generation DES are used. However, to date, there is no evidence that these newer generation stents reduce mortality compared with paclitaxel eluting stents.[36]

Conclusions

In the SYNTAX trial, the largest randomized comparison between CABG and DES-PCI in a broad population of patients with three-vessel or left main disease, we found that CABG is an economically attractive revascularization strategy compared with DES-PCI. However, among patients with anatomically less complex disease, DES-PCI appears to be preferred on both clinical and economical grounds. Finally, we found that the newly developed SYNTAX Score II is a useful discriminator of economic value for revascularisation decisions, providing further support for its incorporation in both clinical guidelines and economic policies.

ACKNOWLEDGEMENTS

We thank Kristine Roy and Els Berenschot-Huijbregts for their administrative assistance, Randall Richner and Mary Ann Clark for their assistance in the design of the study, and Jasper Haverkamp for his assistance in the Dutch costing approach.

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APPENDIX

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Supplementary Table 1. Linear Regression Model for the Prediction of Post-Procedural Length of Stay after Revascularization

Model variable	CABG (n=870)	PCI (n=896)
Intercept	10.2	3.42
Demographics		
Age≥80 years	2.63	-
Female		0.60
Co-morbidities		
Congestive heart failure	3.30	4.79
COPD	-	-
Chronic renal failure, without dialysis	-	8.24
Gastrointestinal bleed or peptic ulcer disease	-	3.17
Complications		
Death	5.11	−4.49
MI	0.57	1.83
Major vascular complications	5.54	0.57
Additional PCI	6.34	2.52
Additional CABG	-	7.85
Pacemaker insertion	9.81	18.86
Post-operative atrial fibrillation	2.84	−1.00
Post-operative infection	3.29	14.08
Post-operative ventricular arrhythmia	-	3.27
Renal failure	5.04	1.27
Respiratory failure	1.84	-
Stroke	3.91	31.7
Cardiogenic shock	-	8.85
Cardiac tamponade	-	−3.49
Transfusion	-	4.42

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention

Supplementary Table 2. EQ-5D Utility Scores by Treatment Assignment

Time Point	CABG	PCI	*p*-value
Baseline	0.693 ± 0.240 [0.729]	0.708 ± 0.242 [0.775]	
1 month	0.737 ± 0.217 [0.807]	0.829 ± 0.198 [0.843]	<0.001
6 months	0.823 ± 0.191 [0.843]	0.840 ± 0.189 [0.843]	0.13
12 months	0.826 ± 0.201 [0.843]	0.832 ± 0.197 [0.843]	0.89
36 months	0.827 ± 0.204 [0.843]	0.821 ± 0.207 [0.843]	0.55
60 months	0.824 ± 0.213 [0.843]	0.822 ± 0.216 [0.843]	0.95

Values in brackets are medians. CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. *P*-values are derived from ANCOVA, adjusted for baseline.

Supplementary Table 3. Regression Model developed from SYNTAX Follow-Up Cost for the Prediction of Long-Term Costs

Parameter	Coefficient Estimate (€)	*p*-value
Intercept	771	0.11
CABG	−348	0.006
Age	10	0.12
Male	−169	0.27
SYNTAX Score 23-32	−361	0.02
SYNTAX Score ≥33	−168	0.28
Left main disease	326	0.01
Peripheral vascular disease	1878	<0.001
Myocardial Infarction during trial	2524	<0.001
Stroke during trial	1705	<0.001

Supplementary Table 4. Regression Model developed from SYNTAX Follow-Up Utility Data for the Prediction of Long-Term Utility Weights

Parameter	Coefficient Estimate	*p*-value
Intercept	0.75337	<0.001
Male	0.10223	<0.001
SYNTAX Score 23-32	0.00277	0.613
SYNTAX Score ≥33	−0.01283	0.02
History of Stroke	−0.02335	0.006
Peripheral vascular disease	−0.04119	<0.001
Carotid artery disease	−0.03535	<0.001
Myocardial Infarction during trial	−0.01307	0.2402
Stroke during trial	−0.08268	<0.001

Supplementary Table 5. Lifetime Cost-Effectiveness Results, incorporating the Impact of MI and Stroke

	Cost, €			QALYs			ICER (€/QALY)	% Dominant	% Dominated	% <€80K
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)				
Base case lifetime analysis (n=1766)	37827	35796	2031 (357, 3499)	11.677	11.279	0.399 (−0.062, 0.800)	5092	0.8	4.6	94.2
LM disease (n=694)	39853	36641	3212 (742, 6155)	10.907	11.350	−0.443 (−1.122, 0.430)	PCI dominant	0.1	79.8	16.8
Three-vessel disease, no LM (n=1072)	36455	35257	1199 (−920, 3183)	12.166	11.233	0.933 (0.283, 1.306)	1284	0.1	14.8	99.8
SYNTAX Score ≤22 (n=562)	38907	37245	1662 (−1660, 4701)	12.400	12.350	0.050 (−0.989, 0.618)	33231	5.9	52.6	33.0
SYNTAX Score 23-32 (n=600)	36108	33538	2570 (−328, 5307)	11.342	11.256	0.086 (−0.596, 0.951)	29969	2.7	30.8	65.5
SYNTAX Score ≥33 (n=595)	38649	36595	2054 (−676, 4623)	11.366	10.227	1.139 (0.386, 1.776)	1803	6.4	0.1	99.8
Difference in 4 year predicted mortality (SYNTAX Score II)										
≥2% in favor of PCI (n=281)	35744	35846	−102 (-4662, 4578)	7.991	9.265	−1.273 (-2.487, 0.138)	PCI dominant	1.3	48.4	3.6
0-2% in favor of PCI (n=235)	37124	33909	3215 (-1286, 7862)	11.420	12.367	−0.947 (-2.816, 0.564)	PCI dominant	0.5	80.5	12.4
0-2% in favor of CABG (n=467)	34854	33965	889 (-1506, 3560)	13.981	13.689	0.291 (-0.597, 1.268)	3055	18.0	14.1	81.3
2-5% in favor of CABG (n=320)	39779	36790	2989 (-1118, 6705)	13.470	12.680	0.790 (-0.375, 1.294)	3783	6.5	10.5	86.7
≥5 in favor of CABG (n=463)	40704	37748	2956 (-301, 6908)	9.719	8.708	1.011 (0.356, 2.002)	2923	3.3	0.3	99.7

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio; LM, left main; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year gained. Costs are discounted at 4%, life-years and QALYs at 1.5% per year.

Supplementary Table 6. Lifetime Cost-Effectiveness Results for Base Case and Sensitivity Analyses, expressed in Terms of Cost per Life Year gained (instead of QALY)

	Cost, €			LYs			ICER (€/LY)	% Dominant	% Dominated	%<€80K
	CABG	PCI	Δ (CABG-PCI) (95% CI)	CABG	PCI	Δ (CABG-PCI) (95% CI)				
Tapered CABG effect between 5 and 10 y										
Life-years instead of QALYs	38164	36235	1929 (252, 3591)	14.359	13.871	0.488 (−0.052, 0.971)	3953	1.3	3.4	96.3
Undiscounted cost and QALYs	38164	36235	1929 (252, 3591)	17.014	16.404	0.609 (−0.042, 1.200)	3167	7.6	2.5	96.6
Incorporate effect of MI and Stroke	37827	35796	2031 (357, 3499)	14.2225	13.6899	0.533 (0.030, 1.264)	3811	0.8	2.7	96.8
Fixed CABG effect between 5 and 10 y										
Life-years instead of QALYs	37823	36235	1588 (−118, 3296)	14.475	13.871	0.604 (−0.087, 1.208)	2629	3.7	3.4	96.2
Undiscounted cost and LYs	37823	36235	1588 (−118, 3296)	17.1591	16.4044	0.755 (−0.088, 1.490)	2103	14.8	1.7	96.6
Incorporate effect of MI and Stroke	37492	35796	1695 (−29, 3208)	14.340	13.690	0.650 (−0.036, 1.235)	2608	2.6	3.0	96.6
No effect of CABG beyond 5 y										
Life-years instead of QALYs	38550	36235	2315 (641, 3975)	14.242	13.871	0.371 (−0.032, 0.746)	6240	0.3	3.2	95.4
Undiscounted cost and LYs	37823	36235	1588 (−118, 3296)	16.870	16.404	0.466 (−0.016, 0.931)	3408	2.7	2.8	96.1
Incorporate effect of MI and Stroke	38205	35796	2409 (779, 3854)	14.1039	13.6899	0.414 (0.017, 0.787)	5819	0.1	2.0	96.9

CABG, coronary artery bypass grafting; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; LY, quality-adjusted life-year gained. Costs are discounted at 4%, life-years and QALYs at 1.5% per year.

Supplementary Table 7. Sensitivity Analysis on Stent Price in Overall Population and SYNTAX Score

Population	Base case with stent price of €935	Required stent price at which the ICER of CABG vs. PCI equals €80,000/QALY gained	Interpretation of sensitivity analysis (other things equal)
Overall (n=1766)	CABG economically attractive	€ −4209	Stent price does not influence economic attractiveness
SYNTAX Score ≤22 (n=562)	PCI dominant	€ 1400	Stent price above this threshold will make PCI economically unattractive*
SYNTAX Score 23-32 (n=600)	CABG economically attractive	€ 675	Stent price below this threshold would make PCI economically attractive
SYNTAX Score ≥33 (n=595)	CABG economically attractive	€ −18340	Stent price does not influence economic attractiveness

***** because of the small difference in QALYs between CABG and PCI, the ICER in the low SYNTAX Score group is strongly depending on the difference in costs.
CABG, coronary artery bypass grafting; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-year gained.

CHAPTER 13

Prediction of Costs and Length of Stay in Coronary Artery Bypass Grafting

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Ann Thorac Surg. 2014;98:2386-93.

ABSTRACT

Background

Although more than 200,000 bypass operations are performed in the U.S. annually, little data exist on the predictors of costs and resource use for this procedure. Questions related to clinical outcomes, costs and resource use in coronary artery bypass grafting (CABG) were addressed.

Methods

In a multi-institutional statewide database, patient level data from 42,839 patients undergoing isolated CABG were combined with cost data. After adjusting for cost-to-charge ratios and inflation, the association of length of stay and costs with the Society of Thoracic Surgeons-Predicted Risk of Mortality (STS-PROM) was analyzed. Patients were randomly divided into a development (60%) and validation (40%) cohort. Regression models were developed to analyze the impact of patient characteristics, comorbidities and complications on post-operative length of stay and total costs.

Results

Post-operative length of stay and total direct costs for CABG averaged 6.9 days and $38,847. Length of stay and costs increased from 5.4 days and $33,275 in the lowest risk decile (mean STS-PROM of 0.6%) to 13.8 days and $69,122 in the highest risk decile (mean STS-PROM 19%). Compared with complications, patient characteristics had little impact on length of stay and costs. Upon validation, the models that combined pre- and post-operative variables explained variance better ($R^2 = 0.51$ for length of stay; $R^2 = 0.47$ for costs) and were better calibrated than the pre-operative models ($R^2 = 0.10$ for length of stay; $R^2 = 0.14$ for costs).

Conclusions

The STS-PROM and pre-operative regression models are useful for pre-operative prediction of costs and length of stay for groups of patients, case-mix adjustment in hospital benchmarking, and pay-for-performance measures. The combined pre- and post-operative models identify incremental costs and length of stay associated with complications and are more suitable for prioritizing quality improvement efforts.

INTRODUCTION

Health care expenditures have increased substantially over the past decades and policy makers try to maintain costs with various measures such as the Affordable Care Act. With the increasing emphasis on efficient medical practice, cardiac surgeons, operating room managers and hospital administrators need to know the implications and predictive power of patient characteristics, comorbidities, and complications on the costs and resource use of open heart surgery. Such information is helpful in planning resource use and can be used for prioritizing quality improvement efforts in high-volume procedures. With almost 1100 procedures per million American adults, coronary artery bypass grafting (CABG) is among the most common performed operations in the world and accounts for more resources expended in cardiovascular medicine than any other single surgical procedure.[1] Little data exist on the predictors of the costs and resource use associated with this procedure.

In this study, clinical data were combined with patient-specific costs for CABG in the Commonwealth of Virginia. Three questions were addressed related to clinical outcomes, costs and resource use. First of all, what are the mean direct costs and length of stay associated with CABG and how is this affected by the predicted risk of operative mortality? Second, how do patient characteristics and specific comorbidities influence the length of stay and direct costs of patients undergoing CABG? And lastly, what is the impact of post-procedural complications on length of stay and total directs costs?

PATIENTS AND METHODS

Study Population

The clinical records of patients undergoing cardiac surgery were prospectively collected in the Virginia Cardiac Surgery Quality Initiative (VCSQI) database. For this project, all isolated, CABGs between January 2003 and April 2013 were selected.

VCSQI is a voluntary consortium of 17 cooperating cardiac surgery centers in the Commonwealth of Virginia.[2] The aim of the collaboration is to improve the quality of cardiac surgical care, while controlling costs. The database captures 99% of all cardiac surgical procedures in the state. VCSQI members contributed their data to The Society of Thoracic Surgeons (STS) Adult Cardiac Database. Each of VCSQI's hospital members agreed in advance to share de-identified patient data for secondary research purposes. This investigation was exempt from formal institutional board review at each participating center because it represents a secondary analysis of the VCSQI data registry in absence

of Health Insurance Portability and Accountability Act patient identifiers. Business Associates Agreements are in place between VCSQI, its 17 member hospitals, and database vendor (ARMUS Corporation, San Mateo CA).

Clinical Data

Clinical data consisted of all the data routinely collected in the STS database. Post-operative outcomes included death, stroke, renal failure, atrial fibrillation, deep sternal wound infection, permanent stroke, prolonged ventilation, and reoperations for bleeding, graft occlusion and other reasons, all defined according to the STS database definitions.[3] In-hospital death was defined as death within 30 days after discharge or within the hospital. Pre-operative risk was assessed with the STS-predicted risk of mortality (STS-PROM). Each institution was accountable for coding and submitting its data to VCSQI's repository and agreed on the definitions, data collection, and timely submission.

Cost and Length of Stay Data

The process of combining clinical and financial data in the VCSQI database has been described elsewhere.[4, 5] Briefly, STS patient records were matched with uniform billing (UB) discharge records, which are used by institutional health care providers throughout the U.S. The UB-04 form replaced its predecessor UB-92 in 2007 and represents the patient's final bill. Charges for all of the ICD-9 (International Classification of Diseases, 9th revision) revenue codes were grouped into 20 logical cost categories (see list in the Appendix). Since charges reflect institutional pricing decisions and other factors unrelated to resource use, we applied cost-to-charge ratios. These ratios were yearly updated and specific for each participating institution and category within that institution. The total costs estimate was the sum of all 20 categories. The medical care service component of the U.S. consumer price index was used to convert all costs to U.S. dollars for the year 2013.[6]

Statistical Analysis

The total cohort consisted of 42,839 patients. Patients were randomly divided into a model development (60%) or model validation (40%) cohort. The two cohorts were analyzed for differences in baseline characteristics, clinical outcomes, and length of stay. Variables were tested for normality using the Kolmogorov-Smirnov test; normally distributed variables were compared using *t*-tests for numerical variables and using chi-squared tests for categorical variables.

Multiple linear regression models with total hospital costs or post-operative length of stay as the dependent variable were built. Separate models were developed: the 2 pre-operative models included only independent variables that were known before the

procedure, whereas the 2 combined models incorporated not only the pre-operative variables, but also outcomes of the procedure, including complications and in-hospital mortality. Given the iterative modeling process and the large number of variables included, only those variables that were significant with a $p \leq 0.01$ were retained in the models. Additionally, the variables age, gender, and race were forced into the models. Regressions were estimated in log and linear form, and reported in linear form, since there were no substantial differences in the results and linear regression coefficients are more easily interpretable. Performance of the models was assessed using the R^2 in the development cohort and by calibration plots in the validation cohort. Trends in plots were presented using polynomials fitted on the entire dataset. Analyses were performed with Excel 2010 (Microsoft, Redmond, WA, USA) and SPSS version 20.0.0 (SPSS, Chicago, IL).

RESULTS

Patient Characteristics, Clinical Outcomes and Costs

Patient characteristics, risk factors, and complications for the development and validation cohort are presented in Table 1. Most CABGs were performed on males that were

Table 1. Variables in the Development and Validation Cohort

Description	Development (n=25,631)	Validation (n=17,208)	*p*-value
Age, yr	64.0±10.7	64.0±10.6	0.70
Male sex	73.7	73.8	0.82
STS-PROM	2.16±3.5	2.19±3.9	0.49
STS-PROMM	13.8±10.5	13.8±10.7	0.93
Race, %			0.04
Caucasian	81.4	81.8	
African American	14.0	13.4	
Hispanic	0.9	0.8	
Asian	2.3	2.5	
Native American	0.1	0.2	
Other	1.3	1.5	
Body mass index, kg/m^2	29.4±5.8	29.3±5.6	0.06
Heart failure ≤2 weeks before, %	12.0	12.0	0.99
Renal failure requiring dialysis, %	2.3	2.3	0.78
Creatinine, mg/dl	1.20±1.0	1.19±1.0	0.77
Left ventricular ejection fraction (SD)	51.3±12.4	51.3±12.5	0.52
Chronic lung disease, %			0.21
No	82.6	82.1	
Mild	10.0	10.1	
Moderate	4.9	5.1	
Severe	2.4	2.7	

Table 1. Variables in the Development and Validation Cohort (*continued*)

Description	Development (n=25,631)	Validation (n=17,208)	*p*-value
Cerebrovascular Disease, %	13.6	13.2	0.24
Pre-operative cardiogenic shock, %	1.6	1.6	0.84
Urgency status, %			0.24
Elective	41.7	41.1	
Urgent	54.6	55.3	
Emergent	3.7	3.5	
On inotropic medication, %	1.6	1.6	0.72
Arrhythmia, %	7.5	7.4	0.93
Myocardial infarction ≤21 days, %	28.9	29.2	0.49
Peripheral arterial disease, %	13.7	13.6	0.46
Hypertension, %	81.1	81.8	0.10
Diabetes Mellitus, %	39.7	39.4	0.52
Immunocompromised status, %	2.1	2.0	0.53
Previous CABG, %	3.1	3.3	0.23
Previous valve operation, %	0.2	0.3	0.15
Previous PCI, %	18.6	18.7	0.82
No. of diseased vessels, %			0.45
One	4.3	4.4	
Two	17.8	17.2	
Three	77.9	78.4	
IABP[e], %			0.40
None	91.5	91.8	
Pre-operative	7.1	6.7	
Intraoperative	1.2	1.2	
Post-operative	0.2	0.2	
Post-operative length of stay, days	6.9±7.3	6.9±.6.7	0.32
Total length of stay, days	9.3±8.1	9.3±7.7	0.84
Post-operative ventilation >24 hours, %	9.3	9.4	0.71
Post-operative renal failure, %	3.5	3.5	0.95
Post-operative pneumonia, %	2.9	2.8	0.47
Post-operative atrial fibrillation, %	17.6	16.8	0.04
Post-operative stroke, %	1.3	1.4	0.47
Post-operative deep sternal wound infection, %	0.5	0.3	0.11
Reoperation bleeding, %	1.7	1.8	0.48
Reoperation other cardiac reasons, %	0.7	0.8	0.42
Reoperation non-cardiac reasons, %	2.0	2.0	0.56
In-hospital mortality, %	1.7	1.8	0.32
In-hospital mortality or morbidity, %	14.4	14.5	0.93

Data defined as mean±SD, or % of patients. IABP, intra-aortic balloon pump; SD, standard deviation; STS-PROM, Society of Thoracic Surgeons-Predicted Risk of Mortality; STS-PROMM, Society of Thoracic Surgeons-Predicted Risk of Mortality or Morbidity; yr, years.

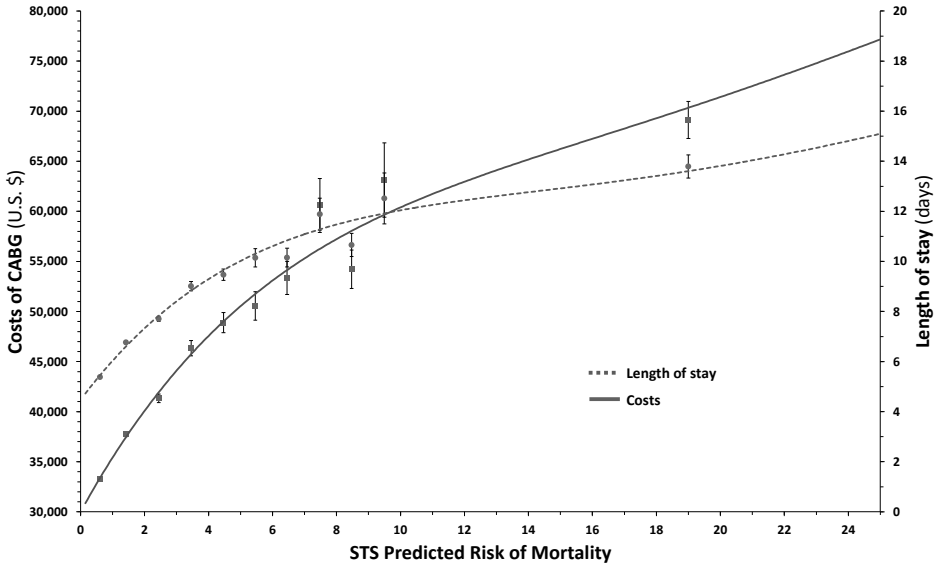

Figure 1. Total Costs and Length of Stay after Isolated CABG according to STS Score
The lines represent polynomial trend lines.
CABG, coronary artery bypass grafting; STS, Society of Thoracic Surgeons.

>60 years old. Atrial fibrillation, prolonged ventilation, renal failure and pneumonia were the most common post-operative complications (17.2%, 9.3%, 3.5% and 2.9%, respectively). There were no clinically important differences in patient characteristics, comorbidities or outcomes between the development and validation cohorts.

Mean length of stay and total direct costs for CABG averaged 6.9 days and $38,847, respectively. Length of stay and costs increased from 5.4 days and $33,275 in the lowest risk decile (mean STS-PROM of 0.6%) to 13.8 days and $69,122 in the highest risk decile (mean STS-PROM 19%; Figure 1). In lower risk patients, length of stay and costs show a similarly increasing trend. In higher risk patients, however, costs increase more rapidly than length of stay.

Length of Stay Regression Models

Multivariable regression results for length of stay are reported in Figure 2A. Of the pre-operative patient characteristics and comorbidities, only 4 out of 30 possible demographic and clinical factors increased length of stay with ≥2 days. A previous valve operation, pre-operative cardiogenic shock, urgent status, and inotropic medication are independently associated with the highest additional length of stay after CABG in the pre-operative model (3.10, 2.49, 2.42 and 2.18 additional days, respectively). In the combined model, predominantly the post-operative complications were associated with considerably longer hospital stay. In this model, the pre-operative variables had either

a small impact or failed to be statistically significant predictors of length of stay. Re-operation for non-cardiac reasons, deep sternal wound infection, and pneumonia were independently associated with the highest additional days in the hospital (12.81, 11.77, and 7.61 additional days, respectively).

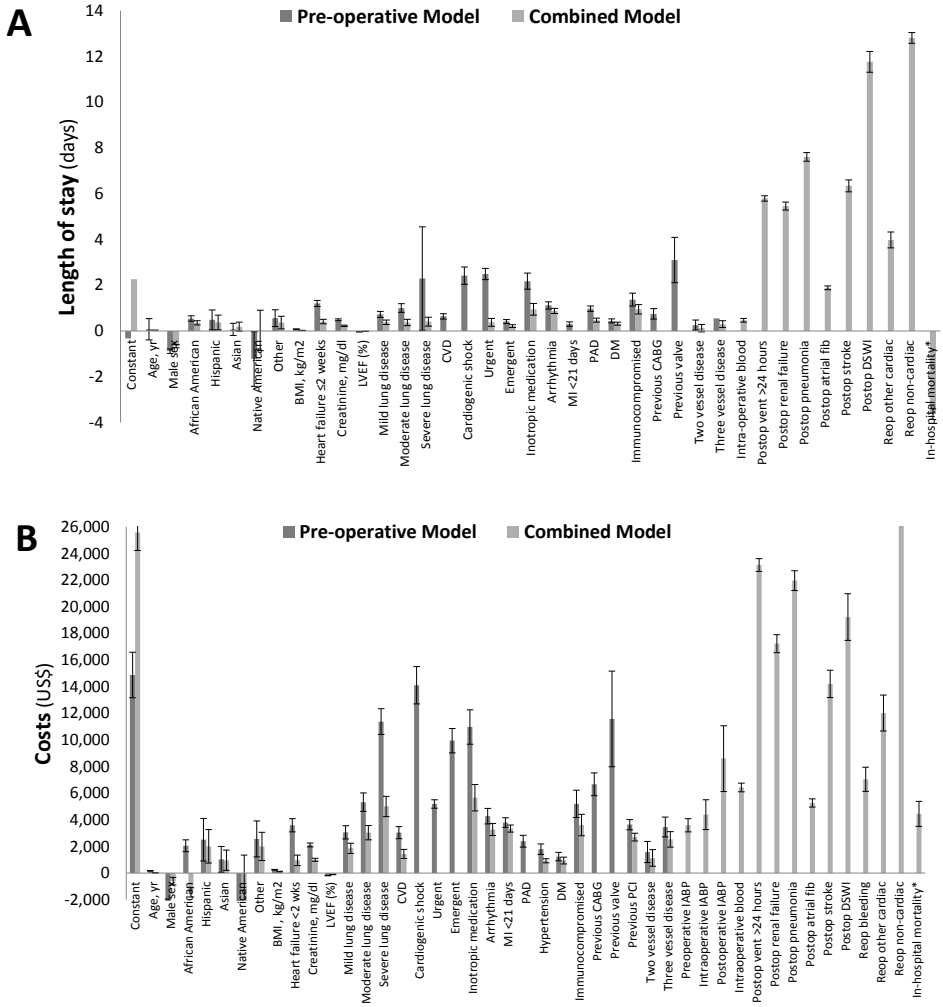

Figure 2. Regression Covariates for Isolated CABG

Multivariable regression results for total costs (A) and length of stay after the procedure (B).
Reference categories are: Caucasian race; no lung disease; elective surgery; one vessel disease; no IABP.
BMI; body mass index; CABG, coronary artery bypass grafting; DM, diabetes mellitus; DSWI, deep sternal wound infection; fib, fibrillation; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; Postop, post-operative; Reop, reoperation; yr, years. * defined as death within 30 days after discharge or within the hospital.

Cost Regression Models

Multivariable regression results for costs are reported in Figure 2B. With respect to the cost prediction models, we observed several relationships similar to those for length of stay. Although a variety of pre-operative variables was associated with higher hospital costs, these variables had a smaller impact when also post-operative complications were taken into account. Pre-operative cardiogenic shock, a previous valve operation and severe lung disease were independently associated with the highest additional costs after CABG in the pre-operative model (additional costs $14,114, $11,597, and $11,376, respectively). For the combined model, complications that were independently associated with the highest additional costs were reoperation for non-cardiac reasons, prolonged ventilation, pneumonia, and deep sternal wound infection ($37,315, $23,127, $21,964, and $19,222 respectively). Except for mortality, which was associated with $4,449 higher costs but 3.64 fewer days in the hospital, there is a large overlap in predictors between the length of stay and cost regression models.

Validation

The R^2 values of the models that only considered pre-operative variables were lower (0.10 and 0.14 for length of stay and costs, respectively) than the R^2 coefficients for models that considered both pre-operative and post-operative variables (0.51 and 0.47 for length of stay and costs, respectively). As expected, the explanatory power of the post-operative models was higher, but a 4- to 5-fold increase in R^2 is perhaps surprising. This suggests that although patient characteristics and comorbidities are important, they are generally not the major drivers of hospital stay and costs.

In the validation cohort, all models showed that they were well calibrated (Figure 3). The absolute difference between observed and predicted length of stay was small across deciles (range 0.0005-0.51 and 0.03-1.02 days for the pre-operative and combined model, respectively). Similarly, the difference between predicted and observed costs was small ($347-$5100 and $10-$5227 for the pre-operative and combined model, respectively). The combined models were slightly better calibrated as they were more consistent with the calibration line (Figure 3).

DISCUSSION

The current study found that the costs (mean $38,847) and post-operative length of stay (mean 6.9 days) associated with CABG are considerable. Length of stay and costs increased from 5.4 days and $33,275 in the lowest risk decile (mean STS-PROM of 0.6%) to 13.8 days and $69,122 in the highest risk decile (mean STS-PROM 19%). To assess how patient characteristics and specific comorbidities influence the length of stay and

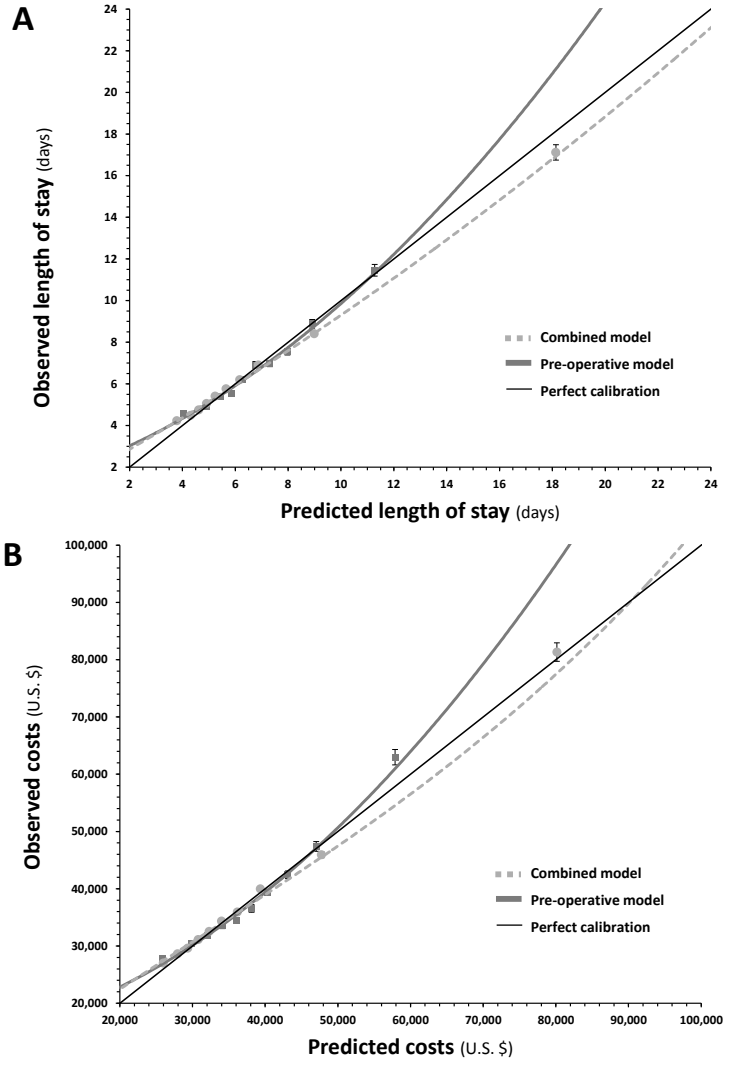

Figure 3. Calibration Plot for Pre-operative and Post-operative Cost (A) and Length of Stay (B) Prediction Models

The green and dashed orange lines represent polynomial trend curves. Error bars represent the standard error of the mean costs of the observed costs (A) or length of stay (B).

direct costs of patients undergoing CABG, 2 length of stay and 2 cost-prediction models for patients undergoing CABG were presented. The pre-operative models were based on patient characteristics and comorbidities known before the procedure; the combined models also incorporated outcomes, complications, and in-hospital mortality. Validation of the models showed that the combined models had 4-5 times more explanatory power but calibration was reasonable in both pre-operative and combined models.

The advantage of the current models is that it presents post-operative hospital length of stay as a continuous variable. Other studies built prediction models only for intensive care stay,[5, 7-10] and categorized their outcome as 'standard' versus 'prolonged', using different definitions. Despite inconsistencies in definitions, variables describing renal function, critical pre-operative state, ejection fraction, inotropic support, and emergencies are important predictors for prolonged intensive care stay. The importance of these predictors is consistent with our models for the prediction of post-operative length of stay.

Few other studies have identified predictors of total hospital costs after cardiac surgery.[11-15] One large retrospective study used Medicare Provider Analysis and Review file data and found a mean cost of $32,201 for CABG in more than 100,000 patients in 2005,[11] but solely focused on the incremental costs of post-operative outcomes. Another study found that both pre-operative and intraoperative variables were predictors of costs in cardiac surgical patients. A model based on pre-operative parameters alone could not explain a reasonable proportion of costs. However, the study consisted of only 201 patients and the financial data seem to be based on charges instead of costs.[13] Riordan and colleagues concluded from their single center study based on of 628 CABG patients from 1997 that contemporary surgical risk models based on pre-operative data were not suitable for cost prediction in individual patients.[12] A recent paper using data from the Nationwide Inpatient Sample on 183,973 CABGs at 633 hospitals between 2005 and 2008 found a very similar mean cost of CABG ($37,924) as in the current manuscript.[15] The study found lower incremental cost of complications, since they included other covariates in their model, such as hospital region, individual hospital effect and length of hospitalization.

The models in this study that combined pre- and post-operative variables have 4-5 times more explanatory power than the pre-operative models. This is reflected by the low R^2 coefficient for the pre-operative model and the fact that many pre-operative variables were no longer significant predictors in the combined model. Complications explained the largest portion of the variation in length of stay and total hospital costs. However, the combined models can only be applied post-hoc and are therefore more suitable for prioritizing quality improvement efforts and assessing the costs of complications. Although the explanatory power of the pre-operative models is smaller and predictions in individual patients inaccurate, the calibration plots show that the pre-operative models can be used to reliably predict the length of stay and costs for cohorts of patients. Figure 1 provides an even easier-to-use tool to instantly estimate the expected length of stay and costs based on the STS-PROM of a group of patients, but also lacks ability for individual patients.

Given the high annual volume of CABG procedures, this type of surgery is a natural target for cost containment and process improvement. For this objective, risk-adjusted length of stay and costs are excellent measures. The pre-operative model will be a useful tool for hospital benchmarking and pay-for-performance measures, better than the combined models since prediction should be adjusted for differences in risk factors and not differences in outcomes.[16, 17]

The ability to identify factors that are the biggest contributors to a long hospital stay and high costs can help clinicians and administrators to focus on areas in which their quality improvement efforts will have the greatest impact. In our models, patient characteristics and comorbidities explained only a small portion of length of stay and costs. Clinicians and hospital management should first focus on reduction of high-frequent, high-cost complications. When prioritizing quality improvement efforts, not only the incremental costs or length of stay of specific complications need to be evaluated (Figure 2), but also the frequency in which they occur (Table 1). Sternal wound infection is a costly (~$19,000) but rare (0.4%) complication, whereas post-operative atrial fibrillation is associated with moderate incremental costs (~$5,000), but occurs much more frequent (17.2%). Consequently, over a 10-year period, the total costs associated with atrial fibrillation were approximately 10 times higher than the costs associated with deep sternal wound infections ($39 million versus $3.4 million, respectively). Other high cost, high frequent complications are prolonged ventilation (~$23,000, 9.3%), pneumonia (~$22,000, 2.9%), and renal failure (~$17,000, 3.5%). Lower complication rates and efficient treatments of these complications will decrease costs.

There are some potential limitations in this study. There might be differences in cost methodology across hospitals, regions and states, since hospital accounting methods, coding and billing patterns differ. By applying category specific, yearly updated cost-to-charge ratios from each participating institution and continuous collaboration within VCSQI, the variation across centers in the Commonwealth of Virginia was minimized. In addition, the current study does not compare outcomes across centers but rather reports summary estimates for all the centers within the state.

In conclusion, CABG is a natural target for cost containment and process improvement, since the annual volume, costs and post-operative length of stay are high. In total, 2 length of stay and 2 cost-prediction models for patients undergoing CABG were presented. The STS-PROM and pre-operative models, which included patient characteristics and comorbidities, are useful for group estimates, case-mix adjustment in hospital benchmarking and pay-for-performance measures. The combined models identify incremental costs associated with complications and can be used for prioritizing quality improvement efforts.

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APPENDIX

Table of Contents

Supplementary Table 1. Cost Categories and ICD-9 Revenue Codes

Cost Category	Revenue Codes
Emergency room	450-459
ICU/CCU	200-219
Regular room	100-179
Radiology	320-359, 400-409
Lab	300-319
Cardiac diagnostics	480, 482-489, 730-731, 739
Peripheral vascular lab	921
Anesthesia	370-379
Operating Room	360-369, 490-499
Recovery room	710-719
Blood products	380-399
Implants (pacers, ICD, valve)	275, 278
General Supplies	270-274, 276-277, 279
Pharmacy	250-259
Intravenous	260-269
Respiratory therapy	410-419
Cardiac catheterization lab	481
Therapies (PT, OT, cardiac rehabilitation)	420-449
Dialysis	800-809, 820-859, 880-889
Other	180-199, 220-249, 280-299, 470-479, 500-679, 700-709, 740-799, 901-920, 922-942, 944-999

CHAPTER 14

Cost, Quality, and Value in Coronary Artery Bypass Grafting

Osnabrugge RL, Speir AM, Head SJ, Jones PG, Ailawadi G, Fonner CE, Fonner E Jr, Kappetein AP, Rich JB.

J Thorac Cardiovasc Surg. 2014; In Press.

ABSTRACT

Objective

Pay-for-performance measures, part of the Affordable Care Act, aim to reduce health care costs by linking value with Medicare payments, but until now the concept of value has not been applied to specific procedures. We sought to define value in coronary artery bypass grafting (CABG) and provide a framework to identify high-value centers.

Methods

In a multi-institutional statewide database, clinical patient-level data from 42,839 patients undergoing CABG were matched with cost data. Hierarchical models adjusting for relevant pre-operative patient characteristics and comorbidities were used to estimate center-specific risk-adjusted costs and risk-adjusted post-operative length of stay. Variation in value across centers was assessed by the correlation between risk-adjusted measures of quality (mortality, morbidity/mortality) and resource use (costs and length of stay).

Results

There were no significant correlations between risk-adjusted costs and risk-adjusted mortality ($r = 0.20$, $p = 0.45$) or morbidity/mortality ($r = 0.15$, $p = 0.57$) across centers. Risk-adjusted costs and length of stay were not significantly associated ($r = 0.23$, $p = 0.37$), because of cost accounting differences across centers. This may explain the lack of correlation between risk-adjusted quality and risk-adjusted cost measures. When risk-adjusted length of stay and morbidity/mortality were used for the framework, there was a strong positive correlation ($r = 0.67$, $p = 0.003$), indicating that higher risk-adjusted quality is associated with shorter risk-adjusted length of stay.

Conclusions

Risk-adjusted length of stay and risk-adjusted combined morbidity/mortality are important outcome measures for assessing value in cardiac surgery. The proposed framework can be used to define value in CABG and identify high-value centers, thereby providing information for quality improvement and pay-for-performance initiatives.

INTRODUCTION

The soaring costs of the U.S. health care system form an increasing burden on society and threaten the financial stability of the government. Currently, health care expenditures represent 10-12% of the gross domestic product in many western European countries and Canada, while this proportion is nearly 18% (almost $3 trillion) in the United States.[1, 2] There is wide consensus that we must contain health care expenditure, while improving quality and numerous approaches focusing on value have been proposed.[3, 4] Pay-for-performance measures and value-based payment modifiers, to be implemented in 2015 as part of the Affordable Care Act, aim to reduce health care costs by linking quality and resource use performance measures with Medicare payments to physicians and hospitals. Physicians will be held accountable for resource utilization and costs for their hospitalized patients.

With more than 200,000 costly procedures performed in the U.S. annually, coronary artery bypass grafting (CABG) is an important procedure for improving health care value.[5] Value can be defined by a combination of clinical quality and resource use and should use risk-adjusted measures.[4, 6] Although comparisons in efficiency exist[7] and quality assessment measures have been proposed,[8-10] the concept of value (combining risk adjusted measures of resource use and quality) has not been applied to specific procedures like CABG.

We conducted a study to define value in CABG and to provide a framework to identify high-value centers. By adjusting for relevant pre-operative patient characteristics and comorbidities, we derived measures of risk-adjusted resource use and risk-adjusted quality after CABG. Subsequently, we tested whether higher risk-adjusted quality was correlated with shorter risk-adjusted length of stay and lower risk-adjusted costs.

METHODS

The Virginia Cardiac Surgery Quality Initiative (VCSQI) database was used for this analysis. Clinical records of patients undergoing cardiac surgery that were prospectively collected and for the current study all primary, isolated CABGs between January 2003 and April 2013 were selected.

VCSQI is a voluntary group of 17 cooperating cardiac surgery centers in the Commonwealth of Virginia.[11] The aim of the consortium is to improve the quality of cardiac surgical care, while reducing costs. The database covers ~100% of all cardiac surgical procedures

in the state. VCSQI members contribute their data to The Society of Thoracic Surgeons (STS) Adult Cardiac Database. Each of VCSQI's center agreed to share de-identified patient data for secondary research and quality improvement. Institutional review boards at each participating center exempted this study because it represents a secondary analysis of the VCSQI data registry in absence of Health Insurance Portability and Accountability Act patient identifiers. Business Associates Agreements are in place between VCSQI, its 17 members, and database vendor (ARMUS Corporation, San Mateo CA).

Clinical Data

Post-operative outcomes were routinely collected in the STS database and included death, stroke, renal failure, atrial fibrillation, deep sternal wound infection, permanent stroke, prolonged ventilation, and reoperations for bleeding, graft occlusion and other reasons, all defined according to the STS database definitions.[12] Operative death was defined as death within 30 days after discharge or within the hospital stay. Pre-operative risk was assessed using the STS-predicted risk of mortality (STS-PROM) and the STS-predicted risk of morbidity or mortality (STS-PROMM). Each center was responsible for coding and submitting its data to VCSQI and agreed on the definitions, data collection, and timely submission.

Cost Data

Patient-level clinical and financial data in the VCSQI database were combined as previously described.[13, 14] Briefly, STS patient records were matched with uniform billing (UB) discharge records. The UB-04 form is used throughout the U.S. and represents the patient's final hospital bill. Charges for all of the ICD-9 (International Classification of Diseases, 9th revision) revenue codes were grouped into 20 logical cost categories (Supplementary Table 1). Since charges reflect institutional pricing decisions and other factors unrelated to resource use, we applied cost-to-charge ratios.[15] These ratios were yearly updated and specific for each participating institution and category within that institution. The total costs estimate was the sum of all 20 categories. The variation in total costs and post-operative length of stay as a result of post-operative complications was reflected in the total estimate for the individual patient.[14] The medical care service component of the U.S. consumer price index was used to convert all costs to U.S. dollars for the year 2013.[13, 16]

Statistical Analysis

We calculated risk-adjusted costs and post-operative length of stay for each of the 17 centers by adjusting for differences in patient case-mix. Risk-adjusted estimates were derived from hierarchical models, which account for clustering of outcomes within hospitals, provide more stable estimates for hospitals with low volumes and adjust for multiplicity of comparisons. This approach to risk-standardization has been gaining in-

creasing traction in recent years and has been adopted by CMS.[17] We modeled cost and post-operative length of stay as dependent variables, applying hierarchical generalized linear models, with a gamma distribution for costs and a negative binomial distribution for length of stay.[18] These models included a random effect for hospital and adjustment for pre-operative patient characteristics and comorbidities (Supplementary Table 2). Given the iterative modeling and large number of variables included, only variables that were significant at a level of $p \leq 0.01$ were preserved in the models.[19] The variables age, gender, and race were forced into the models. The models were recently validated for prediction of post-operative length of stay and costs.[19] Regressions were estimated in log and linear form, and reported in linear form, since there were no substantial differences in the results and linear regression coefficients are more easily interpretable.

Hospital mean risk-adjusted costs were derived by calculating the ratio of average model-predicted costs for a given hospital to the expected costs based only on patient characteristics, and then multiplying this ratio by the overall population-average cost. Hospital mean risk-adjusted lengths-of-stay were calculated in a similar way.[20-22] Risk-adjusted measures of mortality and morbidity/mortality were also calculated per center, based on validated STS risk calculators.

Morbidity/mortality was defined as post-operative deep sternal wound infection, reoperation, permanent stroke, prolonged ventilation, renal failure or operative mortality.[8, 9, 12] Correlation between risk-adjusted quality and resource use measures were assessed with the Spearman's correlation coefficient. Analyses were performed with Excel 2010 (Microsoft, Redmond, WA, USA), SPSS version 20.0.0 (SPSS, Chicago, IL) and the hierarchical models were fitted using the GLIMMIX macro in SAS 9.3 (SAS Institute, Cary, NC.).

RESULTS

The patient characteristics and comorbidities of the 42,839 included CABG patients are presented in Table 1. The STS-PROM averaged 2.2% and the STS-PROMM was 13.8%. Post-operative clinical outcomes and resource use are presented in Table 2. Atrial fibrillation was the most common post-operative complication (17.2%), followed by prolonged ventilation (9.3%) and renal failure (3.5%). Mean total length of stay was 9.3 days of which the majority consisted of post-operative stay (6.9 days). The mean total costs for CABG were $38,848.

There was significant variation in risk-adjusted costs ($27,380 to $55,296), risk-adjusted post-operative length of stay (6.26 to 8.77 days), risk-adjusted mortality (0.95% to

Table 1. Patient Characteristics

Characteristic	N=42,839
Age, yr	64.0±10.7
Male sex	73.7
STS-PROM	2.17±3.7
STS-PROMM	13.80±10.6
Race, %	
Caucasian	81.5
African American	13.8
Hispanic	0.8
Asian	2.4
Native American	0.1
Other	1.4
Body mass index, kg/m²	29.4±5.7
Heart failure ≤2 weeks before, %	12.0
Renal failure requiring dialysis, %	2.3
Creatinine, mg/dl	1.20±1.0
Left ventricular ejection fraction	51.3±12.5
Chronic lung disease, %	
No	82.4
Mild	10.0
Moderate	5.0
Severe	2.5
Cerebrovascular Disease, %	13.5
Pre-operative cardiogenic shock, %	1.6
Urgency status, %	
Elective	41.5
Urgent	54.9
Emergent	3.6
On inotropic medication, %	1.6
Arrhythmia, %	7.5
Myocardial infarction ≤21 days, %	29.0
Peripheral arterial disease, %	14.2
Hypertension, %	81.4
Diabetes Mellitus, %	39.6
Immunocompromised status, %	2.1
Previous CABG, %	3.2
Previous valve operation, %	0.2
Previous PCI, %	18.7
No. of diseased vessels, %	
One	4.2
Two	17.6
Three	78.1

Data defined as mean±SD, or % of patients.
SD, standard deviation; STS-PROM, Society of Thoracic Surgeons-Predicted Risk of Mortality; STS-PROMM, Society of Thoracic Surgeons-Predicted Risk of Mortality or Morbidity; yr, years.

Table 2. Post-operative Clinical Outcomes and Resource Use

Variable	N=42,839
Post-operative ventilation >24 hours	9.3
Post-operative renal failure	3.5
Post-operative pneumonia	2.9
Post-operative atrial fibrillation	17.2
Post-operative stroke	1.4
Post-operative deep sternal wound infection	0.4
Reoperation bleeding	1.7
Reoperation other cardiac reasons	0.8
Reoperation non-cardiac reasons	2.0
Operative mortality	1.8
Operative morbidity/mortality*	14.4
Total length of stay, days	9.3±7.9
Post-operative length of stay, days	6.9±7.0
Total costs [median] ($)	38,848 ± 29,299 [32,397]

Data defined as mean±SD, or % of patients. *defined as: operative deep sternal wound infection, reoperation, permanent stroke, prolonged ventilation, renal failure or mortality.
SD, standard deviation.

2.13%) and risk-adjusted morbidity/mortality (10.78% to 19.44%) across centers. Figure 1A represents a plot of risk-adjusted costs vs. risk-adjusted mortality, showing that there was no statistically significant correlation between risk-adjusted costs and risk-adjusted mortality ($r = 0.20$, $p = 0.45$). Also when complications were included in the risk-adjusted outcome, we found no statistically significant correlation (risk-adjusted costs vs. risk-adjusted morbidity/mortality; $r = 0.15$, $p = 0.57$; Figure 1B).

Figure 2A represents a plot of risk-adjusted post-operative length of stay and risk-adjusted mortality for the 17 cardiac surgical centers. The correlation between risk-adjusted length of stay and risk-adjusted mortality was not statistically significant ($r = -0.27$, $p = 0.30$). This suggests that lower mortality is not associated with lower resource use, as measured by post-operative length of stay.

There was a significant positive correlation between the more comprehensive quality outcome measure risk-adjusted morbidity/mortality and risk-adjusted length of stay ($r = 0.67$, $p = 0.003$; Figure 2B). Also when two centers with the highest risk-adjusted length of stay were excluded, the correlation remained positive and significant ($r = 0.60$, $p = 0.02$). This suggests that higher quality (low risk-adjusted morbidity/mortality) coincides with shorter post-operative length of stay. Those cardiac surgical centers represent high-value CABG. On the contrary, there were also centers in the upper right quadrant

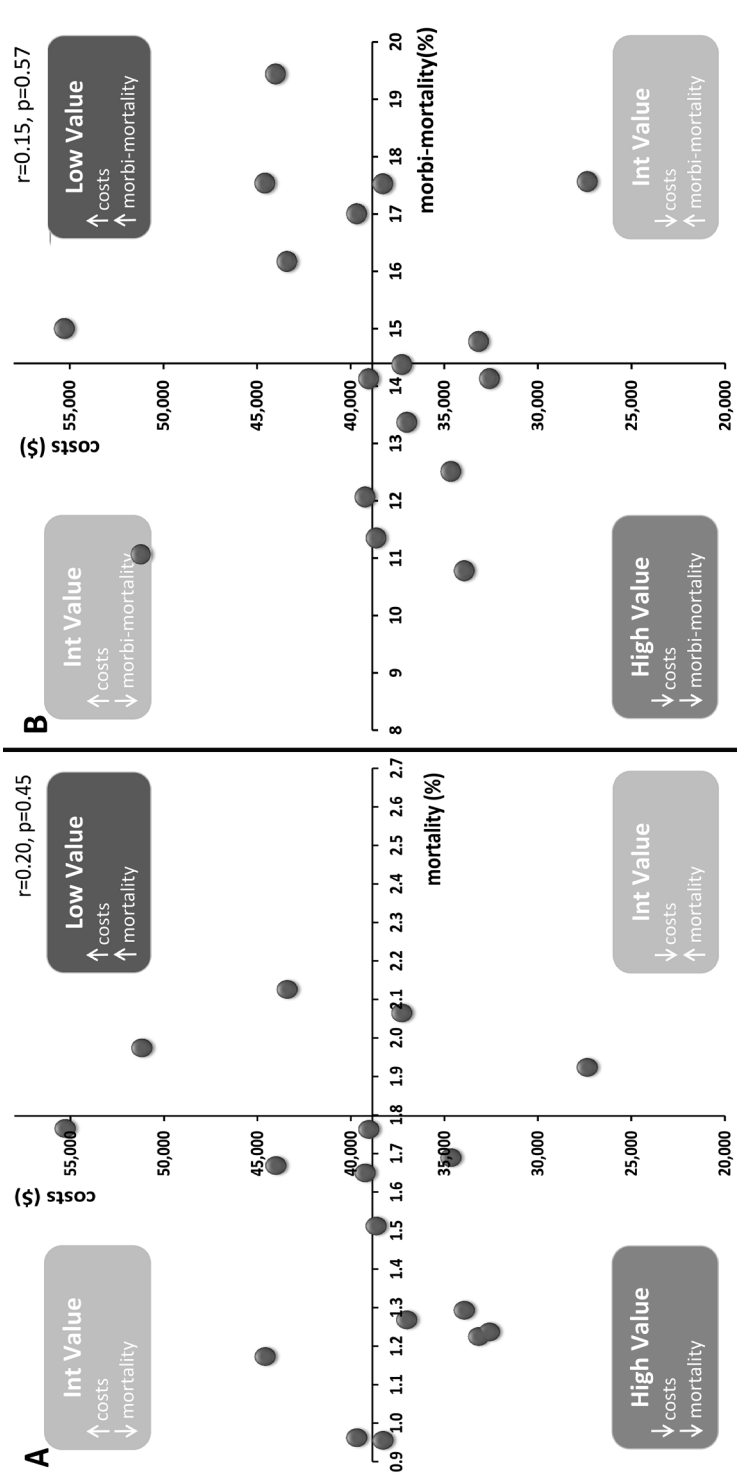

Figure 1. Risk-Sdjusted Costs versus Risk-Adjusted Mortality (A) and versus Risk-Adjusted Morbidity/Mortality (B) per Center
The lack of a statistically significant correlation coefficient indicates that there is no relationship between resource use (risk-adjusted post-operative length of stay) and quality (risk-adjusted mortality and risk-adjusted morbidity/mortality). The axes cross at the population average operative mortality (1.80%) and population average costs ($38,848).
Int, intermediate; LOS, length of stay; r, correlation coefficient.

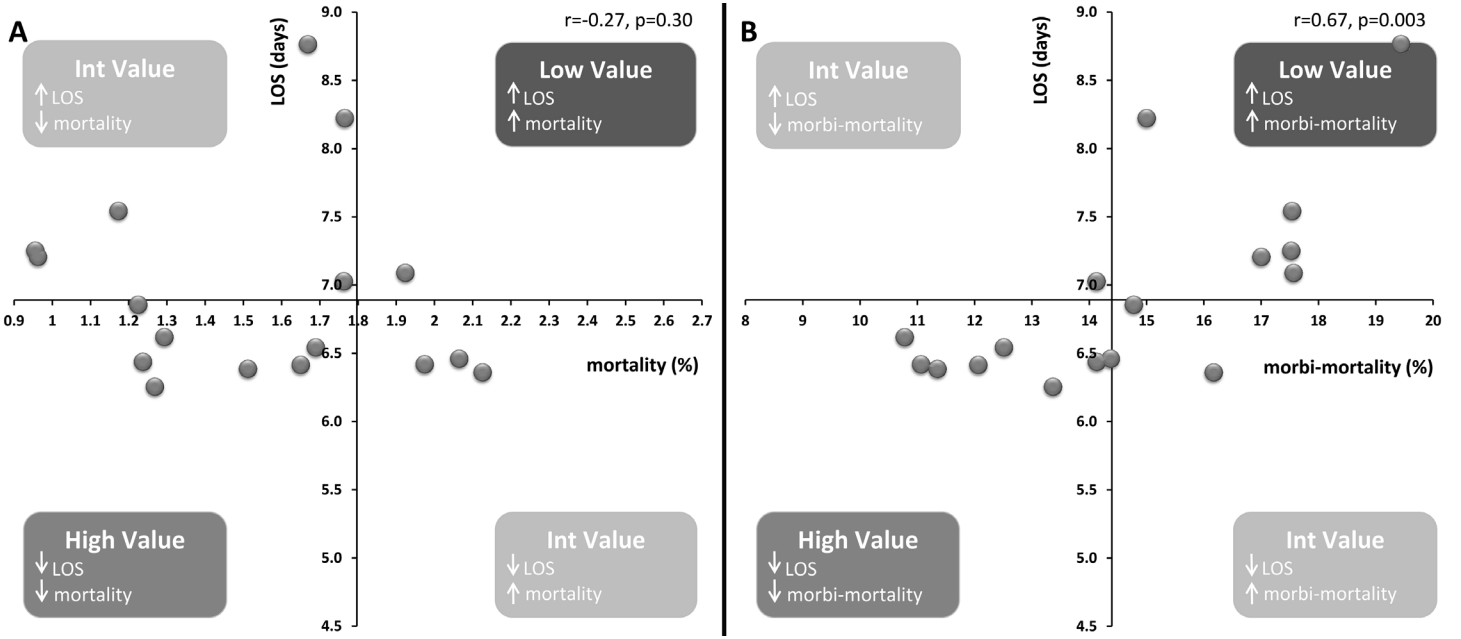

Figure 2. Risk-Adjusted Length of Stay versus Risk-Adjusted Mortality (A) and Risk-Adjusted Morbidity/Mortality (B) per Center

There is no significant correlation between risk-adjusted post-operative length of stay and risk-adjusted mortality. The significant positive correlation coefficient between risk-adjusted length of stay and risk-adjusted morbidity/mortality indicates that centers with higher quality (low risk-adjusted morbidity/mortality) are also more efficient (low risk-adjusted length of stay), thereby representing high-value centers. The axes cross at the population average morbidity/mortality (14.40%) and population average post-operative length of stay (6.9 days).

Int, intermediate; LOS, length of stay; r, correlation coefficient.

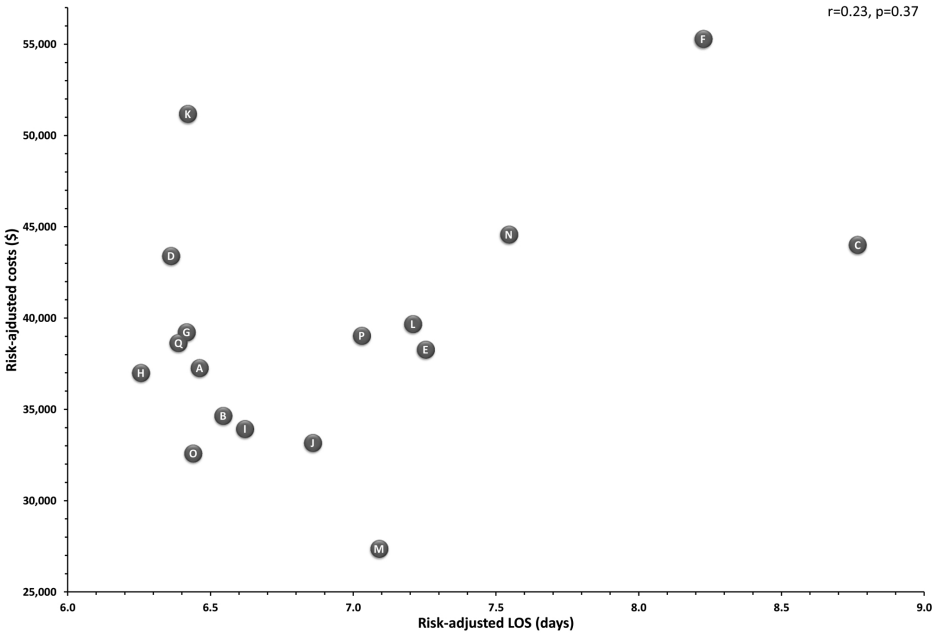

Figure 3. Risk-Adjusted Costs and Risk-Adjusted Length of Stay per Center
The dots represent the risk-adjusted costs (vertical axis) and risk-adjusted length of stay (horizontal axis) per cardiac surgical center.
Int, intermediate; LOS, length of stay; r, correlation coefficient.

which combined high risk-adjusted morbidity/mortality with high risk-adjusted length of stay. This suggests that lower quality, as measured by higher than expected morbidity and mortality, leads to higher resource use, as measured by higher than expected post-operative length of stay. It is these centers that represent low value.

There was no significant correlation between risk-adjusted costs and risk-adjusted length of stay across centers (r = 0.23, p = 0.37; Figure 3). Although there were several centers for which the risk-adjusted costs and risk-adjusted length of stay showed a trend (centers A, O, B, I, J, P, L, E, N), there were also centers (C, K, D and M) that had risk-adjusted costs that was different than would be expected based on risk-adjusted length of stay. Since length of stay is closely related with costs at a group level,[23] a strong correlation between risk-adjusted cost and risk-adjusted length of stay was expected.

DISCUSSION

Even after adjusting for pre-operative patient characteristics and comorbidities, we found important variation in measures of quality (risk-adjusted mortality, risk-adjusted

morbidity/mortality) and resource use (risk-adjusted costs and risk-adjusted length of stay) across 17 centers performing CABG in the Commonwealth of Virginia. A significant correlation existed between risk-adjusted morbidity/mortality and risk-adjusted length of stay. These findings suggest that better quality leads to shorter post-operative length of stay and resource use. Substantial savings and better outcomes can be realized if all centers achieve the same performance of high-value centers.

This is the first study to describe combined center-specific clinical and financial outcomes for CABG. The over- and underperforming centers are shown in the lower left and upper right quadrants in Figure 2B, respectively. The study serves as a basis for discussions on health care value measurement and facilitates improvements of value in health care. Policy measures as pay-for-performance and the value-based payment modifier provide financial incentives to improve value (i.e. to keep costs low by improving outcomes and quality of care).[24, 25] In general, policy measures will provide incentives that relate payment inversely with risk-adjusted clinical outcomes and risk-adjusted resource use. In the current study we found distinct variability in value when both quality and cost measures were combined, but the exact definitions of low/high performers require close collaboration with the physician community before this can lead to real-world payment implications.

Previous studies on pay-for-performance have been criticized for their performance metrics that focused on processes of care that were not clinically meaningful.[26] For instance, measuring the proportion of heart failure patients receiving paper discharge instructions does not necessarily result in better patient outcomes.[27] In general, physicians, patients, and CMS should work together to define meaningful outcome measures. Clinically relevant metrics will not only increase the potential of pay-for-performance but are also more likely to engage physicians than process-based metrics.[28] In the current analyses we used risk-adjusted costs and risk-adjusted length of stay as measures of resource use, and risk-adjusted mortality and risk-adjusted morbidity/mortality as quality measures.

Outcome Measures for Assessing Value

Unexpectedly, we only found a strongly significant correlation when risk-adjusted length of stay and risk-adjusted morbidity/mortality were used as outcome measures for resource use and quality, respectively. Since costs and length of stay are closely related at a group level,[23] we also expected risk-adjusted costs and risk-adjusted morbidity/mortality to be significantly correlated. However, different centers account cost differently, particularly in the way how overhead costs are allocated.[29] A center with brand new facilities and high real estate costs may allocate costs differently to a single procedure (CABG) than centers with depreciated facilities and a lower cost location. This is less of

an issue when the study-objective is to estimate overall costs of a procedure or model building for all centers combined,[19] but using these cost data to compare centers is likely to reflect the variation in accounting systems instead of true differences in the efficiency of performing CABG. Even with a uniform hospital bill (UB-04) and similar cost accounting systems, it is not clear that the accounting practices are comparable across each of the study centers, since also costs of similar resources (catheters, sutures, equipment) might differ between centers. Ideally, standardized unit costs should be applied to each patient's resource consumption,[30] but these data were unavailable for this large dataset.

Our alternative measure of risk-adjusted resource use, length of stay, is widely available and easy to measure. Post-operative length of stay as an isolated performance measure (i.e. without a risk-adjusted quality measure) should be avoided, since this might lead to over-aggressive discharge protocols.[31] Rather a balanced approach to efficiency and quality improvement will provide a patient centric and patient safe approach to health care. Also, factors beyond hospital's direct control (e.g. the lack of post-acute facilities) might influence post-operative length of stay. On the other hand, risk-adjusted length of stay (in combination with risk-adjusted quality) provides incentives for centers to carefully evaluate their processes of care from a broad perspective, including improvements in post-discharge facilities.

We did not find a correlation of risk-adjusted mortality with any measure of risk-adjusted resource use (costs or length of stay). Mortality alone may be an inadequate measure to compare quality across centers and our analyses show that complications are the real driver of the association. Mortality may or may not result in increased resource use since a patient who dies shortly after surgery consumes few resources. Complications on the other hand, always lead to higher resource use consumption. Therefore, the STS Quality Measurement Task Force (QMTF) proposes a comprehensive composite quality score, in which risk-adjusted morbidity/mortality is an important domain.[8, 9]

After high-value centers have been identified, subsequent in-depth research and comparison with low-value centers is needed to identify factors that help explain how these centers achieved the exceptional performance on risk-adjusted quality and risk-adjusted resource use measures. This process of quality improvement could include qualitative research such as collaborative site visits and structured interviews between the participating centers.[8, 9]

Limitations

This study has some limitations. First, the results of this study may not be generalizable to other cardiac surgical centers in the U.S as data were used from 17 cardiac surgical

centers in one state. However, the key variables (STS-PROMM, length of stay) are well-known and therefore, the framework developed in this study can be applied to all cardiac surgical centers in the United States performing CABG. Second, we used post-operative length of stay as a surrogate for resource use since differences in accounting methodology hampered cost comparisons across centers. Ideally, standardized unit costs would have been applied to each patient's resource consumption.[30] However, these detailed individual resource consumption data were unavailable for this large dataset. Instead we used a single measure of resource use, risk-adjusted length of stay, which is closely related with costs at a group level.[23] Third, the study is observational, and unmeasured confounding cannot be excluded. However, the risk-adjustment of length of stay and costs using the available variables was robust, and an observational design is best to evaluate actual clinical practice. Finally, it is important to realize that centers that treat markedly more frail or other special patients might unjustifiably be categorized as a low-value center.

Conclusions

Risk-adjusted length of stay and risk-adjusted combined morbidity/mortality are important outcome measures for assessing value in cardiac surgery. In high-value centers, lower rates of risk-adjusted morbidity/mortality outcomes were associated with shorter risk-adjusted length of stay. The proposed framework can be used to define value in CABG and identify high-value centers, thereby providing useful information for quality improvement and pay-for-performance initiatives.

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APPENDIX

Table of Contents

Supplementary Table 1. Cost Categories and ICD-9 Revenue Codes

Cost Category	Revenue Codes
Emergency room	450-459
ICU/CCU	200-219
Regular room	100-179
Radiology	320-359, 400-409
Lab	300-319
Cardiac diagnostics	480, 482-489, 730-731, 739
Peripheral vascular lab	921
Anesthesia	370-379
Operating Room	360-369, 490-499
Recovery room	710-719
Blood products	380-399
Implants (pacers, ICD, valve)	275, 278
General Supplies	270-274, 276-277, 279
Pharmacy	250-259
Intravenous	260-269
Respiratory therapy	410-419
Cardiac catheterization lab	481
Therapies (PT, OT, cardiac rehabilitation)	420-449
Dialysis	800-809, 820-859, 880-889
Other	180-199, 220-249, 280-299, 470-479, 500-679, 700-709, 740-799, 901-920, 922-942, 944-999

Supplementary Table 2. Pre-operative Patient Characteristics and Comorbidities for which the Cost and Length of Stay Outcomes were adjusted

Cost model	Length of stay model
Age	Age
Male sex	Male sex
Race	Race
Body mass index	Body mass index
Heart failure ≤2 weeks before	Heart failure ≤2 weeks before
Creatinine	Creatinine mg/dl
Left ventricular ejection fraction	Left ventricular ejection fraction
Chronic lung disease (Mild/Moderate/Severe)	Chronic lung disease (Mild/Moderate/Severe)
Cerebrovascular Disease	Cerebrovascular Disease
Pre-operative cardiogenic shock	Pre-operative cardiogenic shock
Urgency status (Urgent/Emergent)	Urgency status (Urgent/Emergent)
On inotropic medication	On inotropic medication
Arrhythmia	Arrhythmia
Myocardial infarction ≤21 days	Myocardial infarction ≤21 days
Peripheral arterial disease	Peripheral arterial disease
Hypertension	-
Diabetes Mellitus	Diabetes Mellitus
Immunocompromised status	Immunocompromised status
Previous CABG	Previous CABG
Previous valve operation	Previous valve operation
Previous PCI	-
No. of diseased vessels (Two/Three)	No. of diseased vessels (Two/Three)

CHAPTER 15

Appropriate Coronary Artery Bypass Grafting Use in the Percutaneous Coronary Intervention Era: are we finally making progress?

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Semin Thorac Cardiovasc Surg. 2012;24:241-3.

ABSTRACT

Appropriate use criteria integrate guidelines, clinical trial evidence and expert opinion to be able to interpret the most appropriate care for a range of distinct clinical scenarios. Inappropriate use estimates cannot be neglected. Approximately 12-14 % of all percutaneous coronary interventions and 1-2% of all coronary artery bypass grafting procedures in patients with stable angina are deemed inappropriate. Several reasons for this striking difference are identified. Continuous improvement of the criteria, multidisciplinary discussions and the correct financial incentives will be essential in reducing the number of inappropriate procedures, improve patient outcomes and contain costs.

The delivery of medical care exhibits substantial regional variations, which cannot be attributed solely to differences in disease prevalence, patient's race or treatment preferences. This variation is present in a wide variety of surgical procedures and certainly exists in the cardiovascular field.[1] In addition, we have seen an unprecedented surge in new medical technologies and treatments for medicine in general, and for the cardiovascular domain in particular. While this opens up new opportunities, rapid adoption of technology is not always justified. Some treatments are only beneficial for selected patients and can be harmful to others. New treatment options often go hand in hand with increased costs and should only be offered to patients who will benefit from them. To ensure the best patient outcomes and keep costs under control, individual patient care has to be performed according to latest evidence and guidelines.

The selection of the best treatment option is not straightforward, since individual patients have a myriad of characteristics which do not completely align with the guidelines or with the selected patient groups in clinical trials. The method for determining appropriateness aimed to overcome this by integrating guidelines, clinical trial evidence and expert opinion into an appropriateness scale of a certain procedure for a range of distinct clinical scenarios.[2]

Recently, the American College of Cardiology Foundation updated their appropriate use criteria (AUC) for coronary revascularization.[3] Coronary revascularization was deemed appropriate when the expected benefits, in terms of survival or health outcomes, exceeded the expected negative consequences of the procedure.[3] In more detail, the appropriateness of a procedure in distinct clinical scenarios was scored on a scale from 1 to 9 by a technical panel. Procedures were deemed appropriate, uncertain or inappropriate. In the uncertain category more evidence or information on the patient was needed.

Several studies have used the AUC to assess the inappropriate use of PCI and CABG. Recent large registries found rates of inappropriateness of approximately 12% to 14% and rates of uncertain appropriateness of 38% to 50%.[4, 5] Interestingly, the more PCI facilities there are available per number of inhabitants, the more PCIs are performed.[6] For CABG, an early study showed that 16% of the procedures were inappropriate.[7] More recent evidence from large registries suggest a reduction in inappropriateness to 1-2%.[5, 8] Together the inappropriate revascularization procedures account US$1 to $10 billion additional health care costs.[9] A focus on eliminating inappropriate revascularization could therefore not only provide better outcomes for patients, but significantly reduce costs in an era of increasing health care expenditures.

The difference in rates of inappropriateness between CABG and PCI are striking and several reasons can be identified. First of all, patients' perceptions and the extensiveness of physicians' explanations about the benefits and risks of the revascularization method may have an influence on rates of inappropriateness.[10] The invasiveness of CABG might persuade patients to request PCI. Also, patients value the early and benefit of PCI higher than the long term advantages of CABG (temporal discounting).[11]

A second reason might be that PCI can be performed as an ad-hoc procedure during the same visit as the diagnostic catheterization, leaving little opportunity for multidisciplinary involvement and considerations.[12] CABG on the other hand is often performed after referral and with more than one physician participating in the decision. Interestingly, patients who were more suitable for CABG after coronary angiography were more likely to be recommended surgery when the angiography was performed at hospitals without the ability to perform ad hoc PCI.[13] Also, the quality of life results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, led to reconsideration of medical therapy in patients with stable angina.[14]

It seems clear that pay-for-performance incentives might play a prominent role in inappropriate revascularization. While it may indeed be important, it is challenging to hypothesize that a physician focusses on his own interests when treating a patient. Moreover, ad-hoc stenting is performed more frequently in academic hospitals as compared with general hospitals.[12] A more important problem might be the fact that the guidelines and practicing cardiologists are not aligned. In a Medscape survey, 43% of the 645 interviewed cardiologists stated that guidelines have a negative impact on patient care.[15] Belief in AUC is even lower with 75% of the cardiologists stating that criteria and quality measures had either no or even a negative impact on patient care. These results should be an incentive to bring the practicing cardiologists and the societies who make the guidelines closer together.

In dealing with inappropriateness, a multidisciplinary heart team can play a crucial role. Such a team consists of at least a non-interventional cardiologist, an interventional cardiologist and a cardiovascular surgeon and is currently recommended in the European and American revascularization guidelines, as well as in the AUC of the American College of Cardiology Foundation.[3, 16, 17] With the joint effort of different specialties and stakeholders, the patient is more likely to undergo a treatment based on the guidelines and latest evidence. Patients will also be better informed and value the elaborate evaluation of their treatment. To fully benefit from the heart team, clinical and financial aspects of the decision-making process need to be aligned. For instance, in the Netherlands the heart team discussions are reimbursed and in academic hospitals the physician's income is not

directly related to the number of procedures performed. In this way, decisions will be fully based on the evidence for the specific patient and financial incentives do not get the chance of playing a role. Salaries should be based on the quality of care provided and not on the number of procedures.

Despite continuous efforts to improve the criteria, some important limitations of AUC persist.[18] Inappropriate indications show only moderate concordance between a range of cardiologists and the AUC technical panel.[19] This makes the composition of the relatively small (n = 17) technical panel essential and weakens the validity of AUC studies. Moreover, the number of clinical scenarios is limited, the role of pre-procedural diagnostic testing is unclear and the interpretation of the uncertain and inappropriate categories is confusing.

On the other hand, the AUC have moderate to very good reliability and good construct validity.[20] Care deemed appropriate was also a predictor of better outcomes as compared with care deemed inappropriate.[20] Interestingly, there were eminent practice variations even within a New York State's PCI registry. This means that even though AUC scenarios are criticized by interventional cardiologists.[18] they do not seem to have consistency as a group with regard to how to treat patients.[5]

Altogether, inappropriate use cannot be neglected. Continuous improvement of the criteria, multidisciplinary discussions and the correct financial incentives will be essential in reducing the number of inappropriate procedures, improve patient outcomes and contain costs.

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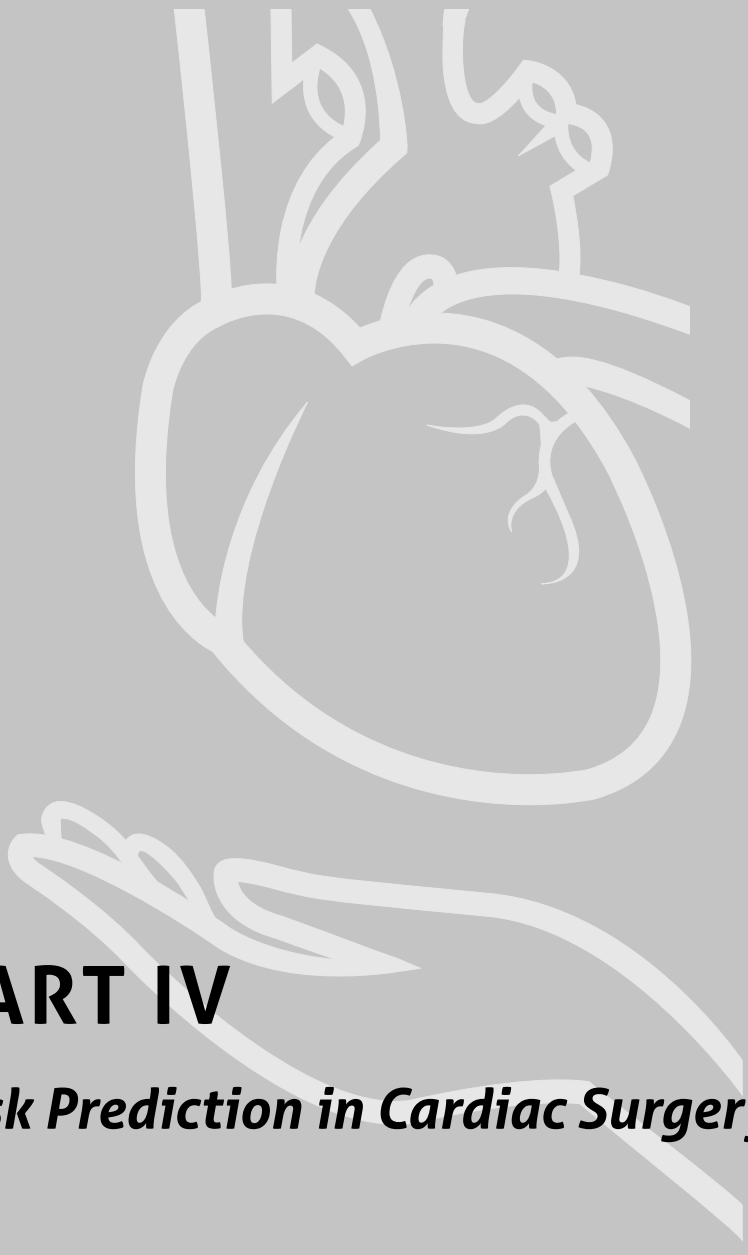

PART IV

Risk Prediction in Cardiac Surgery

CHAPTER 16

Performance of EuroSCORE II in a large US Database: Implications for Transcatheter Aortic Valve Implantation

Winner of the 2013 EACTS Young Investigator's Award – Cardiac

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Eur J Cardiothorac Surg. 2014;46:400-8.

ABSTRACT

Objective

Validation studies of the EuroSCORE II have been limited to European datasets. Therefore, the aims of this study were to assess the performance of the EuroSCORE II in a large multicenter U.S. database, and compare it with the Society of Thoracic Surgery Predicted Risk of Mortality (STS-PROM). In addition, implications for patient selection for transcatheter aortic valve implantation (TAVI) were explored.

Methods

The EuroSCORE II and STS-PROM was calculated for 50588 patients from a multi-institutional statewide database of all cardiac surgeries performed since 2003. Model performance was assessed using the area under the receiver operator curve (AUC), observed versus expected (O:E) ratios and calibration plots. Analyses were performed for isolated CABG (n = 40871), AVR (n = 4107), AVR+CABG (n = 3480), mitral valve (MV) replacement (n = 1071) and MV repair (n = 1059).

Results

Overall in-hospital mortality was 2.1%. The EuroSCORE II was outperformed by the STS-PROM in the overall cohort with regard to discrimination (AUC=0.77 versus 0.81, respectively; $p < 0.001$) and calibration (O:E = 0.68 versus 0.80, respectively). Discrimination for CABG was worse with the EuroSCORE II (AUC=0.77 versus STS-PROM 0.81, $p < 0.001$). For other procedures discrimination was similar: AVR (AUC=0.71 versus STS-PROM 0.74, $p = 0.40$), AVR+CABG (AUC=0.72 versus STS-PROM 0.74, $p = 0.47$, MV repair (AUC=0.82 versus STS-PROM 0.86, $p = 0.55$), and MV replacement (AUC=0.78 versus STS-PROM 0.79, $p = 0.69$). Calibration of the EuroSCORE II was worse for CABG (O:E = 0.68 versus STS-PROM 0.80), similar in AVR+CABG (O:E = 0.76 versus STS-PROM 0.70) and MV Repair (O:E = 0.64 versus STS-PROM 0.67), while EuroSCORE II may be more accurate in AVR (O:E = 0.96 versus STS-PROM 0.76). Performance of both models improved when only recent cases (after January 1st 2008) were used. Ongoing TAVI trials aimed at patients with an estimated 4-10% risk of mortality are enrolling patients with mean estimated risks of 6.2% (EuroSCORE II) or 6.0% (STS-PROM), and an actual mortality of 4.6% (EuroSCORE II) or 4.8% (STS-PROM).

Conclusions

In a large U.S. multicenter database, the STS-PROM performs better than the EuroSCORE II for CABG. However, the EuroSCORE II is a reasonable alternative in low-risk CABG patients and in those undergoing other cardiac surgical procedures. Clinical trials and physicians that use these scores, recruit and treat patients that are at a lower risk than anticipated. This potentially leads to overtreatment with an investigational device. Decision-making should not solely be based on risk scores, but should comprise multidisciplinary heart team discussions.

INTRODUCTION

Risk models are essential for clinical decision-making, benchmarking of clinical practices, and patient-selection in clinical trials. Several scores are currently used in cardiac surgery.[1] The widely utilized EuroSCORE predicts 30-day mortality after cardiac surgery.[2] It was developed in 1999 using a dataset of almost 15000 patients and updated in 2003.[2, 3] Validation studies of the EuroSCORE have shown that the score over-predicts mortality, especially in high-risk patients.[4, 5] The EuroSCORE II was introduced to improve performance and increase applicability to contemporary cardiac surgery.[6] It was derived from a database of 23000 patients who underwent cardiac surgery in 43 countries in the year 2010.

The new score seems to perform better than the original score, but validation studies have been limited to European datasets.[7-13] With increasing transatlantic research collaboration and the potential benefits of using the more parsimonious EuroSCORE II also in the U.S., knowledge on the performance and comparability of this score in North-American patients is essential. For instance, two major multinational trials currently investigate transcatheter aortic valve implantation (TAVI) as an alternative to surgical aortic valve replacement (AVR) in intermediate risk patients (Clinicaltrials.gov identifier: NCT01586910 and NCT01314313).

These trials use the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) for patient selection, whereas the EuroSCORE is used in everyday practice in Europe. Therefore, the purpose of this study was to compare the performance of the EuroSCORE II with the STS-PROM model in a large multicenter U.S. database, and also explore implications for patient selection for TAVI.

METHODS

Study Population

Clinical records of patients undergoing cardiac surgery were prospectively collected from 2003 to 2012 in the Virginia Cardiac Surgery Quality Initiative (VCSQI) database. For this study, all patients who underwent isolated coronary artery bypass grafting (CABG), isolated AVR, isolated mitral valve (MV) replacement, isolated MV repair, or CABG+AVR were selected. VCSQI is a voluntary consortium of 17 cardiac surgical centers providing cardiac surgery in the Commonwealth of Virginia. The database captures 99% of all cardiac surgical procedures.[14] VCSQI members contributed data to the STS Adult Cardiac Database. Data analyses were exempt from the University of Virginia Institutional Review

Board, because patients were de-identified and the fact that the data were primarily collected for non-research purposes.

Definitions and Risk Score Calculation

Operative mortality was defined as i). death during initial hospital stay, or ii). death within 30 days if the patient is discharged <30 days. The EuroSCORE II was built using death during the initial hospital stay,[6] and therefore we performed additional analyses using that endpoint definition. Because EuroSCORE II performance was similar (discrimination) or better (calibration) using the operative mortality definition, we report all comparative analyses based on that definition. Moreover, using the same endpoint definition facilitates the comparison in this U.S. cohort of patients. Patient characteristics, risk factors and other variables were collected using STS database definitions. Some definitions were not totally equivalent to the EuroSCORE definitions. Critical pre-operative state was assessed combining the variables resuscitation, inotropes use, ventricular tachycardia or fibrillation and pre-operative intra-aortic balloon pump for hemodynamic instability. Creatinine clearance was calculated using the Cockroft-Gault formula,[15] and where only the mean pulmonary artery pressure was collected, we calculated the systolic pulmonary pressure using the formula reported by Kind et al.[16] No data was available for poor mobility due to musculoskeletal dysfunction and consequently the EuroSCORE II risk factor 'poor mobility' was based on neurological dysfunction only.[11] The Canadian Cardiovascular Society (CCS) class was not scored for each individual patient and therefore we used the variable unstable angina as a proxy. Patients were assumed to be New York Heart Association (NYHA) class 1 if congestive heart failure was absent. Subsequently, the logistic EuroSCORE and EuroSCORE II were calculated for each patient,[3, 6] while the STS-PROM had been routinely calculated at the time of data entry in the database. Since patient risk factors and case-mix in adult cardiac surgery change dynamically over time,[17, 18] sensitivity analyses were performed to investigate whether model performance was better in more recent procedures. Based on an analysis of predicted risk and mortality profiles over time, recent cases for the sensitivity analyses were defined as procedures after January 1st 2008.

Statistical Analysis

Baseline characteristics are displayed as proportions or means ± standard deviation for discrete and continuous variables, respectively. The risk models were evaluated in terms of discrimination and calibration, using the area under the receiver operator curve (AUC) and calibration plots. An AUC of 1.0 indicates perfect discriminative power, whereas 0.5 indicates no discriminative abilities. AUCs were compared using the method proposed by Hanley et al.[19] Calibration represents the agreement between observed outcome and predicted outcome. The Hosmer-Lemeshow test was not used, since it is not informative in large samples. Instead, we compared observed in-hospital mortality with expected

in-hospital mortality. We constructed calibration plots of observed versus expected mortality, displaying the trend using Friedman's super-smoother methodology on the ungrouped data.[20] In addition, we divided the cohort into 10 equally sized groups based on the ranked predicted risk.

Analyses were performed for all procedures combined, as well as per procedure. Patients who underwent AVR were also classified into low, intermediate or high operative risk, according to their predicted risk of mortality (0-4%, 4-10% and >10%, respectively). These STS-PROM cutoffs are used in ongoing TAVI vs. surgical AVR trials (Clinicaltrials.gov identifiers: NCT01586910 and NCT01314313). Analyses were performed with SPSS for Windows (version 20.0.0.1; IBM, Armonk, NY, USA) and R software (version 2.15.3).

RESULTS

Patients

Full patient characteristics are presented in Table 1. The mean age of the population was 64.7 years and 14622 patients (28.9%) were women. The majority (40871) of the 50588 patients included during the study period underwent CABG. Other procedures were isolated aortic valve replacements (AVR, 4107 patients), combined AVR+CABG (3480) procedures, isolated MV repairs (1059 patients), and isolated MV replacements (1071 patients). The mean values of the STS-PROM, EuroSCORE II, and logistic EuroSCORE were 2.7%, 3.2%, and 6.9%, respectively. Overall operative mortality was 2.1% (1071 patients).

Overall Performance of the Scores

Figure 1 presents the AUC of the different risk prediction models in the overall cohort of patients. The STS-PROM had better discriminatory power compared to the EuroSCORE II (AUC=0.81 versus 0.77, respectively; $p < 0.001$) and logistic EuroSCORE (AUC=0.81 versus 0.78, respectively; $p = 0.003$). The AUC of the EuroSCORE II and logistic EuroSCORE were similar (AUC=0.77 versus 0.78, respectively; $p = 0.16$).

The calibration curves of the STS-PROM, EuroSCORE II and logistic EuroSCORE are presented in Figure 2. All scores showed a relatively linear relationship between predicted and observed mortality. The scores were below the perfect prediction line, meaning that they over-predicted mortality. In patients with a predicted risk of mortality above approximately 5%, the STS-PROM was better calibrated than the EuroSCORE II. The logistic EuroSCORE considerably over-predicted in-hospital mortality in all patients. Expressed numerically, the EuroSCORE II, STS-PROM and logistic EuroSCORE had an observed versus expected (O:E) ratio of 0.68, 0.80, and 0.32, respectively (Table 2).

Table 1. Patient Characteristics

Characteristic	N=50 588
Age (mean ± SD)	64.6 ± 11.2
Female	14 622 (28.9)
Body mass index (mean ± SD)	29.7 ± 7.9
Renal function	
Moderately impaired (CC 50-85 ml/min)	19 152 (37.9)
Severely impaired (CC <50 ml/min)	7 032 (13.9)
On dialysis	1 256 (2.5)
Extracardiac arteriopathy	6 887 (13.6)
Poor mobility	1 700 (3.4)
Previous cardiac surgery	3 544 (7.0)
Chronic pulmonary disease	3 948 (7.8)
Active endocarditis	312 (0.6)
NYHA class	
NYHA 1	19 852 (39.3)
NYHA 2	9 274 (18.3)
NYHA 3	14 875 (29.4)
NYHA 4	6 587 (13.0)
Pulmonary hypertension	
Moderate (31-55 mm Hg)	7 280 (14.4)
Severe (>55 mm Hg)	1 620 (3.2)
Recent myocardial infarction	19 001 (37.6)
Critical pre-operative state	1 904 (3.8)
Diabetes on insulin	5 571 (11.0)
CCS class 4 angina	18 169 (35.9)
Left ventricular ejection fraction	
Moderate (31-50%)	10 284 (20.3)
Poor (21-30%)	3 030 (6.0)
Very poor (≤20)	1 274 (2.5)
Type of procedure	
Isolated CABG	40 871 (80.8)
Isolated AVR	4 107 (8.1)
Isolated MV replacement	1 071 (2.1)
Isolated MV repair	1 059 (2.1)
CABG + AVR	3 480 (6.9)
STS-PROM score (mean ± SD)	2.7 ± 4.2
EuroSCORE II (mean ± SD)	3.1 ± 5.0
Logistic EuroSCORE (mean ± SD)	6.7 ± 8.3

Values are number of patients (%) unless otherwise indicated. AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CC, creatinine clearance; CSS, Canadian Cardiovascular Society; MV, Mitral Valve; NYHA, New York Heart Association; SD, standard deviation; STS-PROM, Society of Thoracic Surgery Predicted Risk of Mortality.

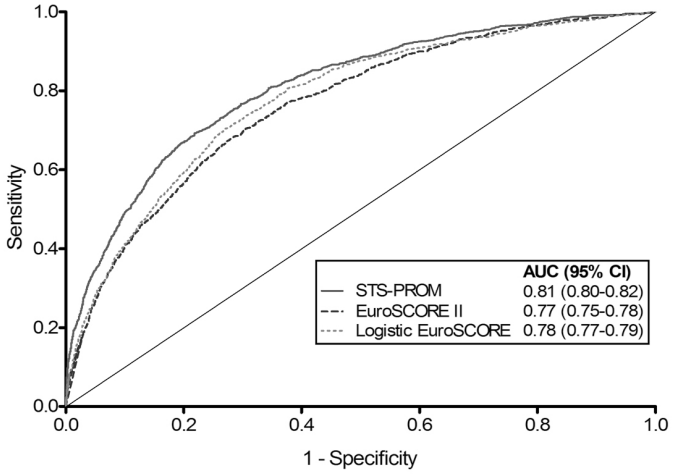

Figure 1. Receiver-Operating Curves of Risk Models for the Overall Cohort
The diagonal line represents no discriminatory power (AUC = 0.50). The higher the AUC, the better is the discriminatory power. AUC: area under the curve; CI: confidence interval; log: logistic.

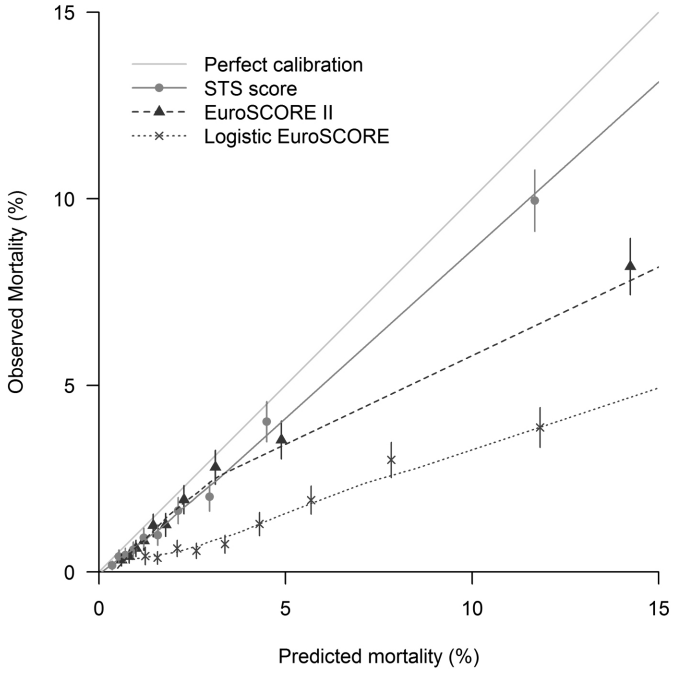

Figure 2. Calibration Plots of Risk Models for the Overall Cohort
The diagonal line represents perfect calibration. Calibration of EuroSCORE II and the STS-PROM is good and similar up until a predicted in-hospital mortality rate of 5%. For patients with a predicted morality >5%, the STS-PROM is better calibrated. The logistic EuroSCORE over-predicts mortality across all patients. Vertical bars represent 95% CIs. Log: logistic

Table 2. Performance in the Overall Cohort and in Different Types of Procedures

Procedure	STS-PROM Score					EuroSCORE II					AUC comparison
	n	Mort (%)	Score	AUC (95% CI)	O:E (95%CI)	n	Mort (%)	Score	AUC (95% CI)	O:E (95%CI)	*p*-value
All procedures	50 558	2.12	2.65	0.81 (0.80-0.82)	0.80 (0.75-0.85)	50 558	2.12	3.14	0.77 (0.75-0.78)	0.68 (0.63-0.72)	<0.001
CABG	40 871	1.80	2.18	0.81 (0.79-0.83)	0.83 (0.77-0.89)	40 871	1.80	2.94	0.77 (0.75-0.79)	0.61 (0.56-0.66)	<0.001
AVR	4 107	2.90	3.84	0.74 (0.69-0.78)	0.76 (0.62-0.89)	4 107	2.90	3.02	0.71 (0.67-0.75)	0.96 (0.79-1.13)	0.40
AVR+CABG	3 480	4.11	5.85	0.74 (0.70-0.78)	0.70 (0.59-0.82)	3 480	4.11	5.38	0.72 (0.68-0.76)	0.76 (0.64-0.89)	0.47
MV repair	1 059	1.32	1.96	0.86 (0.77-0.95)	0.67 (0.32-1.03)	1 059	1.32	2.07	0.82 (0.76-0.89)	0.64 (0.30-0.97)	0.55
MV replacement	1 071	5.60	6.50	0.79 (0.74-0.85)	0.87 (0.65-1.09)	1 071	5.60	4.59	0.78 (0.72-0.83)	1.22 (0.91-1.52)	0.69

AUC, area under the curve; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CI, confidence interval; Mort, mortality; MV Mitral Valve; n, number of patients; O:E, observed versus expected ratio for in-hospital mortality.

Performance according to Type of Procedure

The calibration of the STS-PROM and EuroSCORE II according to the type of procedure is presented numerically in Table 2 and graphically in Figure 3. Isolated CABG was the most common procedure and performance of the STS-PROM and EuroSCORE II was similar to their performance in the 'all procedure' category. Both scores showed good calibration up until approximately 5% of the predicted risk of mortality; after that, the STS-PROM was better calibrated than the EuroSCORE II (Fig. 3A). Discrimination in CABG patients was better with the STS-PROM model than with the EuroSCORE II (AUC=0.81 versus 0.77, respectively; $p < 0.001$).

For patients who underwent AVR, the STS-PROM over-predicted mortality in almost a linear fashion (Fig. 3B). The EuroSCORE II under-predicted in low risk patients, while it also showed over-prediction in higher risk patients. The O:E ratios according to pre-defined risk categories showed a similar picture (Table 3). The STS-PROM over-predicted relatively similarly across risk categories(O:E ratios, low 0.76, intermediate 0.79, and high 0.71); the EuroSCORE II under-predicted in low risk patients, and over-predicted in intermediate and high risk patients (O:E ratios, low 1.51, intermediate 0.74 and high 0.51, respectively). Discrimination in patients who underwent AVR was similar between scores (AUC=0.74 for STS-PROM versus 0.71 for EuroSCORE II; $p = 0.40$).

Both the STS-PROM and EuroSCORE II performed equivalent in patients undergoing combined AVR+CABG procedures, although the EuroSCORE II was slightly better calibrated in lower risk patients (Fig 3C). Calibration in high risk patient was poor in both scores. Discrimination in patients undergoing AVR+CABG was similar for both scores (AUC=0.74 for STS-PROM versus AUC=0.72 for EuroSCORE II; $p = 0.47$).

The calibration plots for MV procedures showed a sizeable amount of uncertainty (Fig. 3D and Fig. 3E). There were only 116 patients with a EuroSCORE II>4% in the MV repair group,

Table 3. Calibration in AVR according to Risk Category

Procedure	STS-PROM Score				EuroSCORE II			
	n	Mort (%)	Score	O:E	n	Mort (%)	Score	O:E
AVR								
Low risk	2911	1.44	1.92	0.76 (0.62-0.89)	3435	2.15	1.42	1.51 (1.17-1.86)
Intermediate risk	923	4.77	6.02	0.79 (0.56-1.03)	459	4.58	6.20	0.74 (0.42-1.05)
High risk	273	12.09	16.95	0.71 (0.47-0.96)	213	11.27	21.93	0.51 (0.31-0.72)

AUC, area under the curve; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CI, confidence interval; Mort, mortality; MV Mitral Valve; n, number of patients; O:E, observed versus expected ratio for in-hospital mortality. Risk categories were classified as 0-4, 4-10 and >10 for low, intermediate and high risk respectively.

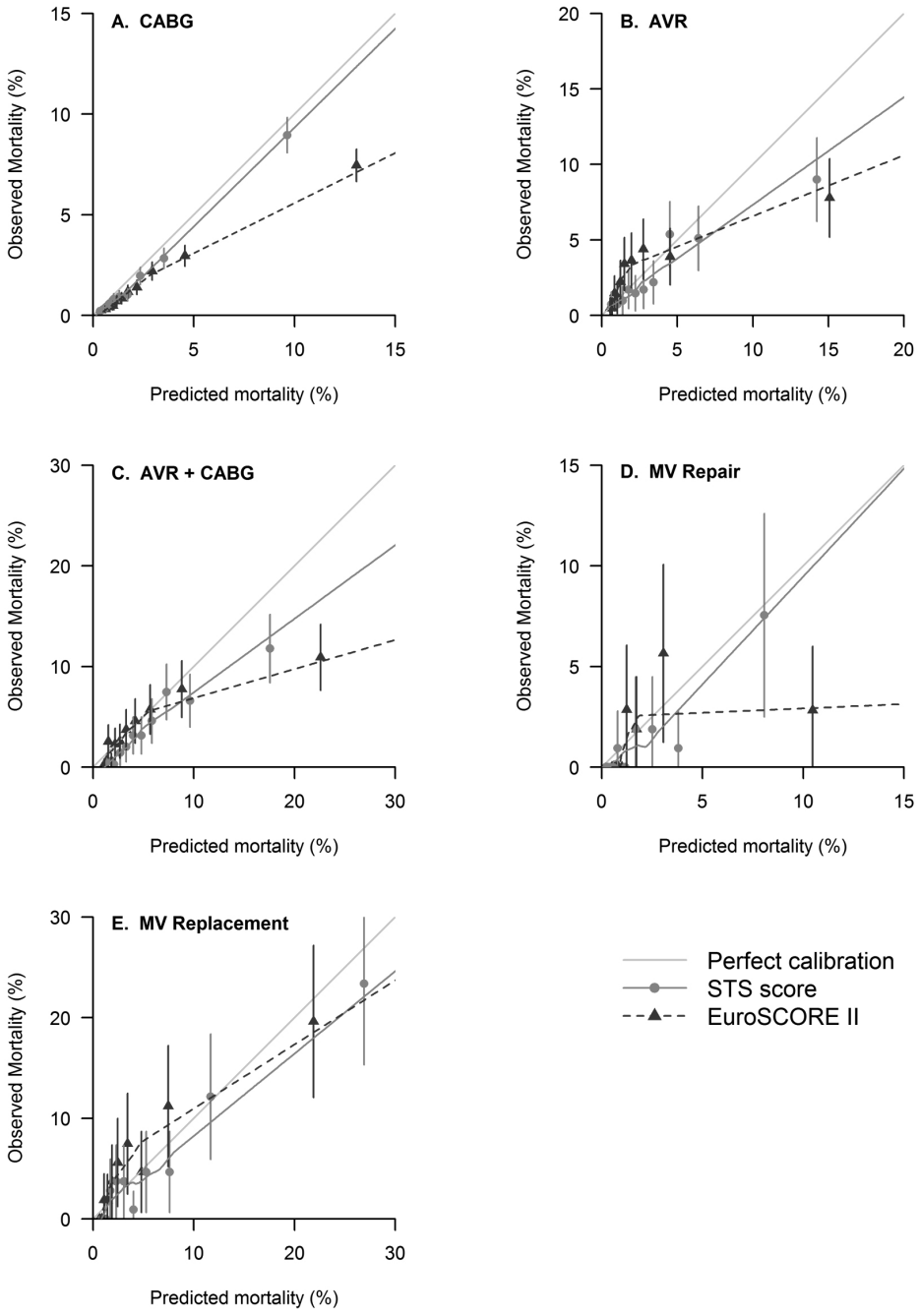

Figure 3. Calibration Plots of Risk Models according to Type of Procedure
The diagonal line represents perfect calibration. Vertical bars represent standard errors of the mean. AVR, aortic valve replacement; CABG, coronary artery bypass grafting; MV, mitral valve

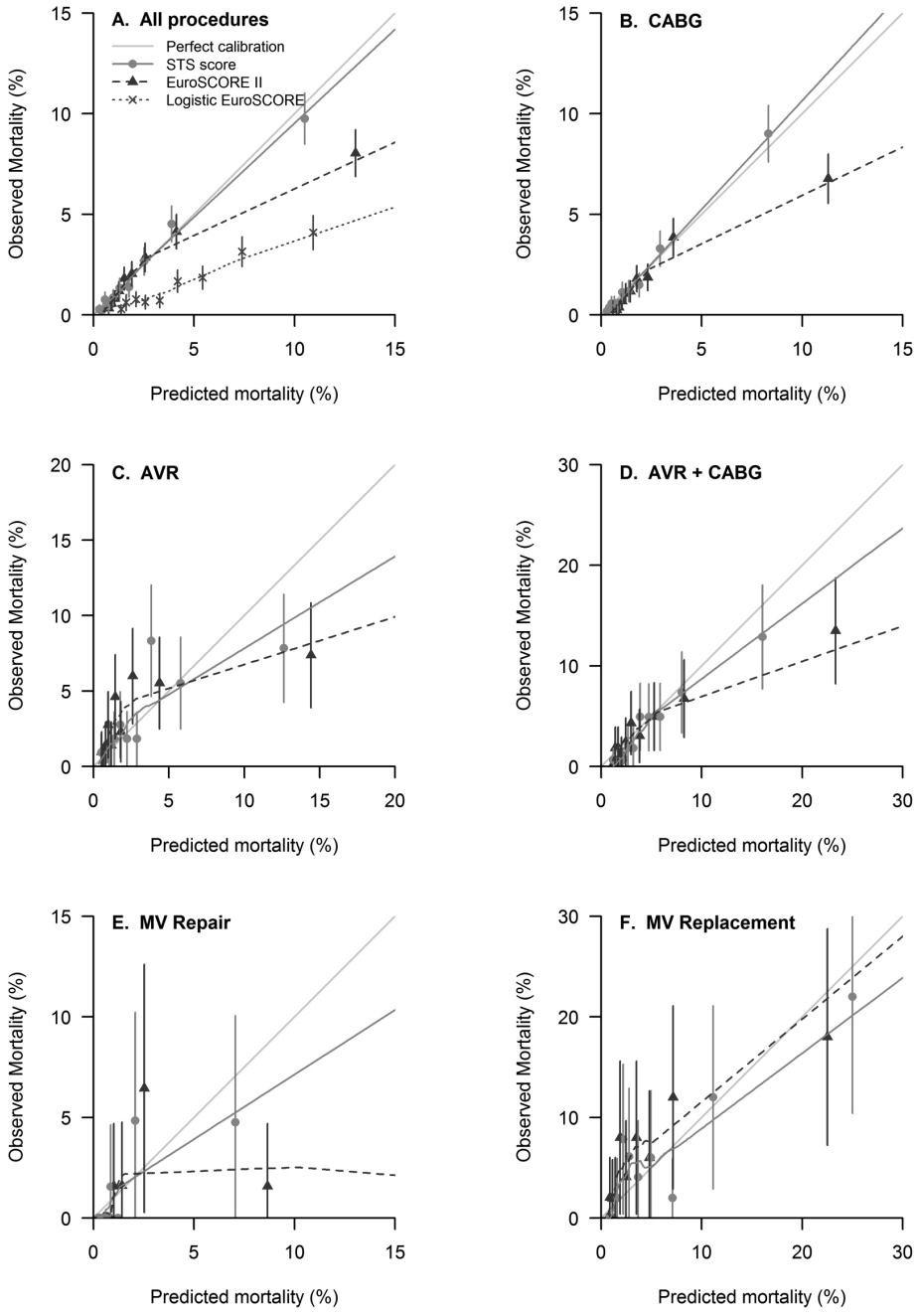

Figure 4. Calibration Plots of Risk Models for the Overall Cohort and according to Type of Procedure, including only Surgeries performed after January 1st 2008

The diagonal line represents perfect calibration. Vertical bars represent standard errors of the mean. AVR, aortic valve replacement; CABG, coronary artery bypass grafting; log, logistic; MV, mitral valve

Table 4. Performance in Recent Cases*

Procedure	STS-PROM Score					EuroSCORE II					AUC comparison
	n	Mort (%)	Score	AUC (95% CI)	O:E (95%CI)	n	Mort (%)	Score	AUC (95% CI)	O:E (95%CI)	*p*-value
All procedures	21016	2.22	2.31	0.81 (0.78-0.83)	0.96 (0.87-1.05)	21016	2.22	2.77	0.76 (0.74-0.78)	0.80 (0.73-0.87)	0.004
CABG	16096	1.82	1.83	0.81 (0.78-0.83)	0.99 (0.88-1.11)	16096	1.82	2.49	0.77 (0.74-0.80)	0.73 (0.65-0.81)	0.05
AVR	2170	3.27	3.28	0.72 (0.66-0.77)	1.00 (0.76-1.22)	2170	3.27	2.88	0.69 (0.63-0.75)	1.14 (0.87-1.40)	0.59
AVR+CABG	1627	4.00	4.95	0.76 (0.71-0.81)	0.81 (0.61-1.00)	1627	4.00	5.23	0.74 (0.68-0.80)	0.76 (0.58-0.95)	0.94
MV repair	624	1.12	1.37	0.87 (0.78-0.97)	0.87 (0.21-1.42)	624	1.12	1.75	0.83 (0.76-0.90)	0.64 (0.17-1.11)	0.49
MV replacement	499	6.21	6.03	0.74 (0.65-0.83)	1.03 (0.67-1.39)	499	6.21	4.63	0.74 (0.65-0.82)	1.34 (0.87-1.81)	0.95

*Cases performed after January 1st 2008.

AUC, area under the curve; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CI, confidence interval; Mort, mortality; MV Mitral Valve; n, number of patients; O:E, observed versus expected ratio for in-hospital mortality.

leading to difficulties in making inferences on higher risk patients. In low risk patients, EuroSCORE II tended to under-predict mortality, whereas the STS-PROM tended to over-predict. Also discrimination with the STS-PROM and EuroSCORE II was similar (AUC=0.86 versus 0.82, respectively; $p = 0.55$). Among patients that underwent MV replacement, 330 patients had a EuroSCORE>4%, but substantial variances in O:E ratios hinder inferences on the calibration of both scores. Discrimination was similar (AUC=0.79 for STS-PROM versus AUC=0.78 for EuroSCORE II; $p = 0.69$).

Sensitivity Analysis of Recent Cases

The sensitivity analysis showed that both the STS-PROM and EuroSCORE II were better calibrated) in a more recent patient cohort (Table 4, Fig. 4). Calibration improved for both the STS-PROM and EuroSCORE II in the overall cohort (O:E = 0.96 and 0.80, respectively), in isolated CABG (O:E = 0.99 and 0.73, respectively). Especially in low risk recent CABG patients both scores are well calibrated. The STS-PROM improved for low risk AVR and AVR+CABG procedures (Fig. 4C and Fig. 4D). The small samples of patients who underwent MV repair or MV replacement resulted in disparate calibration results. Discrimination was similar across procedures, scores, and time (Table 2, Table 4).

DISCUSSION

This is the first study that validated the EuroSCORE II in a large multicenter U.S. database and compared its performance with the STS-PROM across a range of cardiac surgical procedures. Overall, the STS-PROM was better calibrated and was superior in discriminating patients that were likely to survive cardiac surgery from those who were more likely not to survive. Nevertheless, the performance of the EuroSCORE II was satisfactory, especially in recent low risk CABG and non-CABG procedures. In patients who underwent AVR, both STS-PROM and EuroSCORE II over-predicted mortality. These findings have implications for clinical decision-making, outcome comparisons, and research practices.

Several studies have reported reasonable performance of EuroSCORE II.[7-13] Two of them compared the performance with the STS-PROM.[7, 12] Kirmani et al. used data from more than 15 000 patients who underwent CABG, valve surgery or a combined procedure.[12] They concluded that both models provide equivalent discrimination, and that calibration is good in patients with a predicted risk of mortality <15%. Differences with the current results are most likely caused by the different underlying patient population. The STS-PROM and its variables are routinely collected, scrutinized and calculated in the U.S., whereas this is not the case in the majority of European centers.

There are several reasons for the better performance of the STS-PROM compared with the EuroSCORE II. First of all, the STS-PROM was created using datasets that were much larger than the development datasets of the EuroSCORE II. The CABG model of STS-PROM version 2.61 was based on almost 500,000 patients, whereas the development cohort of the EuroSCORE II comprised less than 8000 CABG patients.[6, 21] In addition, the EuroSCORE II dataset contained data from 43 countries ranging from China to Sudan, whereas the STS-PROM database only comprises U.S. centers. Moreover, the STS models used more elaborate statistical methods to deal with missing data. Taking these methodological considerations into account, the performance of the EuroSCORE II is still satisfactory; the differences with the STS-PROM are relatively small and calibration is even largely similar in low risk patients, which is the most common patient group in everyday clinical practice.

The current results support the importance of frequently updating risk scores. The sensitivity analysis of recent cases showed that the calibration of both models improved when applied to contemporary practice. Whereas the STS-PROM score is regularly updated, the EuroSCORE II was essentially the first update after the additive and logistic versions that were based on data from 1995.[2, 3, 6] The poor calibration of the original EuroSCORE has been reported elaborately and was confirmed again in this study.[5] The update makes the EuroSCORE II better applicable to current practice. Operative techniques, patients, and general clinical management change over time and have an impact on outcomes. These developments cannot be neglected when developing and applying risk models.

The advantage of the EuroSCORE II is that it is easier to calculate. Whereas the STS-PROM contains more than 40 variables, the EuroSCORE II requires only 18 variables.[22] Some studies even suggest that it could be further simplified by removing 8 variables, without sacrificing performance.[8] A parsimonious model is more user-friendly, less resource-intensive and is more likely to be used in settings where risk scoring and collection of documentation of variables is not obligatory.

Implications for TAVI

Risk models are a method of standardizing inclusion into trials across different study sites in different countries. Although not designed for TAVI, the STS-PROM and EuroSCORE are currently used in several studies that investigate TAVI in patients with severe AS. Two major ongoing multinational trials compare TAVI with surgical AVR in patients at intermediate operating risk: the PARTNER 2 and SURTAVI trials.[23] These trials use a STS-PROM >4% to select intermediate risk patients. The validity of this method depends on the precision of these models to correctly identify the intermediate risk populations. Our study shows that the STS-PROM over-predicts mortality in these patients (O:E = 0.79 in intermediate and 0.71 in high risk patients). Dewey et al. found similar over-prediction by

STS-PROM in high-risk AVR patients (O:E = 0.71),[4] and Osswald et al. showed a significant over-prediction by the old logistic EuroSCORE (O:E = 0.20).[24] Barili et al. compared the EuroSCORE II with the STS-PROM in patients that underwent isolated AVR and found that it was associated with worse discrimination, but better calibration as compared with the STS-PROM.[7] Both scores had a tendency of under-prediction in higher risk patients in this dataset of 1758 Italian patients, of which a small proportion was at high risk. In the total dataset only 25 (1.4%) patients died, which makes inferences regarding discrimination and calibration in the small high risk group less reliable. We found that the EuroSCORE II over-predicts mortality in intermediate and high risk patients, and that its calibration is similar to the STS-PROM (O:E = 0.74 in intermediate and 0.51 in high risk patients).

If solely selected on the basis of these scores, patients are in fact at lower risk than anticipated. The mean STS-PROM in cohort A of the PARTNER trial was 12, which corresponds to an actual mortality of 8.5% (O:E = 0.71 in high-risk patients).[25] TAVI trials aimed at patients with an estimated 4-10% risk of mortality are actually enrolling patients with mean estimated risks of 6.0% (STS-PROM) or 6.2% (EuroSCORE II). Relying exclusively on risk scores may introduce bias in the interpretation of the study results due to model limitations. While underestimation leads to more conservative patient selection, overestimation leads to potentially recruiting patients for an investigational therapy, while they might be better off with conventional AVR with well-established efficacy and long-term results.

Also in everyday clinical practice, decision-making should not be based solely on risk scores. There are several factors that are not included in the risk scores, but might be very important for outcomes: frailty, vessel tortuosity, porcelain aorta, chest wall malformation or chest radiation. Recently, gait speed was added to the updated STS-PROM as a proxy for frailty. New risk models that incorporate these variables are being developed, but need to be validated.[23]

A multidisciplinary heart team approach is essential to combine risk scores, clinical judgment and these additional aspects. Over the past years, multidisciplinary decision-making has gained more attention in the cardiovascular community. The team includes a cardiac surgeon, interventional cardiologist, clinical cardiologist, nurse practitioner and specialists in imaging, heart failure, cardiac rehabilitation. Physicians have become accustomed to this approach and it is recommended to select the optimal treatment strategy for patients with aortic stenosis, both in everyday practice and in clinical trials.[23]

Implications for Outcome Comparisons across Centers

There is an increasing interest in comparative clinical outcomes analyses and performance in high risk (cardiac) surgery is likely to be an important quality indicator. These

analyses require robust models to adjust for case-mix. However, our study shows that using the STS-PROM or EuroSCORE II in certain patient groups is inappropriate because of inadequate calibration. While the excellent calibration of the STS-PROM in recent CABG surgery allows for robust risk-adjustment, the limited performance in other procedures should be taken into account when comparing outcomes across centers. More specifically, comparison of outcomes in high risk patients is troublesome due to common miscalibration in these patients.[13]

Limitations

Definitions were based on the STS database, and for the EuroSCORE II, some assumptions based on clinical judgment and combinations of other variables had to be made. Prospective studies, collecting all the variables exactly according to their EuroSCORE II definitions are needed to overcome this limitation. Also, the STS-PROM was calculated at time of data entry, whereas the EuroSCORE II was calculated retrospectively. Therefore, we cannot rule out that the performance of the EuroSCORE II is an underestimation. Comparability with other validation studies of the EuroSCORE II is not hampered, since they also had a retrospective nature and applied similar assumptions. Although we performed a sensitivity analyses based on risk and mortality profiles over time, there is the possibility of dynamic changes in case-mix and risk factors influencing the results.[17, 18]

Another limitation is that risk models and the current manuscript focus on short-term mortality. Although the optimal timeframe for the mortality outcome is contentious, a validation study like ours should use the same outcome measure as the development study.

CONCLUSION

In a large U.S. multicenter database, the STS-PROM performs better than the EuroSCORE II for CABG. However, the EuroSCORE II is a reasonable alternative in recent low-risk CABG patients and in those undergoing other cardiac surgical procedures. For AVR, both models over-predict mortality. Clinical trials and physicians using these scores recruit patients that are at a lower risk than anticipated, potentially leading to overtreatment with an investigational device. Decision-making should not solely be based on risk scores, but should comprise multidisciplinary heart team discussions.

ACKNOWLEDGEMENT

We are thankful to Philip Jones MS for his statistical assistance.

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APPENDIX

Conference Discussion, EACTS 27th Annual Meeting in Vienna, October 2013

Dr W.T. Brinkman (Dallas, TX, USA): The authors are to be complimented on the arduous task of trying to go through and reconcile these two disparate risk models. As you point out, the STS-predicted risk mortality is based on 500,000 patients, while the EuroSCORE II is 23,000 patients. In the STS-predicted risk, the mortality contains one of the 40 variables, while in the EuroSCORE it is 18. And in fact, the STS database is soon going to expand to include more variables to take into account important factors such as cirrhosis, calcification of the aorta, things like that.

So proper risk stratification is critical with the advent of new disruptive technologies such as TAVR. Currently, the FDA in the United States limits the application of TAVR to non-operative and high-risk patients. To broaden the use of TAVR in the US, clear risk stratification is mandatory. Trials such as SURTAVI and PARTNER II were designed with these questions in mind, as you brought up. So in the light of all that, I have some questions.

My first question. When calculating your STS risk score, if the New York Heart Association classification was absent, you assumed it was Class I. That seemed to me to be an important factor in a patient with a valve disease. So what was the absent rate in valve patients where you were just assuming Class I? And might that be a problem for calculating the STS risk, seeing how the New York Heart Association is a strong variable in the STS calculation?

Dr Osnabrugge: What we did with the NYHA class is important. When you calculate the STS score online and you click on "Congestive Heart Failure," you'll get a pop-up box where you can fill in the NYHA class. If you say okay, there is no congestive heart failure, then you don't get that box, and that's why we felt comfortable to say it was absent in those cases.

For the specific AVR subgroup, I don't know the absent rate exactly for this subgroup. I would have to go back to the data. But, in line with my first answer, I think we felt comfortable to assume Class I when NYHA was missing.

Dr Brinkman: Okay. My next question. Your data does support the STS for being superior in performance of all procedures and CABG, and your data was 80% CABG. So, with only 7% of AVR in your study group and a non-significant difference between the AUC comparisons between the STS and the EuroSCORE, do you really think that proves that EuroSCORE II is a reasonable alternative to the STS, and is there enough power to really make that statement? Dr Osnabrugge: Well, of course, we would like to have more patients, but I think this is the largest AVR group in which the STS score and the EuroSCORE

II have been compared. So I think it's the best data there is. And, yes, of course, even more patients would have been better.

Dr Brinkman: Okay. One final question. In our cardiac surgery clinic in Dallas, on a daily basis, we calculate the STS for all our patients. It is required for a lot of reasons, and especially for inclusion in trials such as PARTNER II and SURTAVI, and it is not a big deal for us to go and use the online tool. It takes us just a few minutes. We don't use the EuroSCORE. Could you tell me why we should be calculating the EuroSCORE?

Dr Osnabrugge: Well, that's a great question. Less is more, maybe. The EuroSCORE II only has 18 variables. And if the performance is similar, I think it would be a good idea to also calculate the EuroSCORE II. But more importantly, it is also nice to have the EuroSCORE II to compare your patients to patients who are included in studies in Europe. It results in a better comparison when you look across the Atlantic.

Dr D. Pagano (Birmingham, U.K.): I have a comment and a question for you. The comment is that it is quite clear now that we have a paradox. If you look at the isolated, first-time coronary artery bypass grafting, the mortality is so low for in-hospital mortality or short-term outcome, that you almost don't need risk stratification consistently for mortality. The question is about the high-risk group. There is a common thread here. The groups in which it is very important to make a clinical decision, particularly when there are alternatives, are the groups in which the risk algorithms perform badly. Have you got an idea why that may be the case, and how would you improve that?

Dr Osnabrugge: The question is, why in the high-risk patients are the scores performing badly? There are always fewer patients in this higher-risk category, so the estimates become unstable. It is unfortunate, but we have less data on these patients.

Dr Pagano: Can I have the opportunity of asking Fred what he thinks about this issue, because it is a fundamental issue?

Dr F.H. Edwards (Chicago, IL, USA): First of all, I think it is a great question, and I agree with your answer. Yes, you've got smaller numbers once you get up into that higher spectrum. For years at STS we've talked about just accumulating those high-risk patients and making a separate risk model devoted specifically to those higher-risk patients. And over the years, we would have enough numbers, I think, to be able to obviate the problem that you point out. So we're going to try to do that. In the meantime, I think we're just left with exactly the situation that you describe and, again, I think your answer to it is perfect.

Dr J. Gummert (Bad Oeynhausen, Germany): One more question. Could you speculate, if you were to make the same analysis in European patients comparing EuroSCORE II and STS score, could it be possible that the difference you've seen reflects maybe differences in the different healthcare systems, in terms of indication, in terms of treatment policies?

Dr Osnabrugge: It is difficult to really pinpoint that that would be the reason. There has been, off the top of my head, one other study which looked at this. They got similar results with slightly fewer patients. That was a European data set, and the overall conclusion was similar.

Dr N. Van Mieghem (Rotterdam, the Netherlands): First of all, I wanted to mention when you determined the STS score and you didn't know the New York Heart Association class, if it was I, II, or III, does that not change the score? That is to begin with. And then the other thing is, it is very difficult to compare risk models if you do not use the same definitions. For instance, peripheral arterial disease is defined differently in EuroSCORE and STS. So did you take that into account?

Dr Osnabrugge: It is difficult, and that is definitely a limitation of this comparison. That is the only thing I can say about it. And with regard to the first question on NYHA class, this is more of a problem if you want to calculate the EuroSCORE II and you have to include the NYHA class there, that is where the problem arises. Not in the STS score, because it is included there sort of automatically.

CHAPTER 17

A Systematic Review of Risk Prediction in Adult Cardiac Surgery: Considerations for Future Model Development

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Eur J Cardiothorac Surg. 2013;43:e121-129.

ABSTRACT

Objective

Risk prediction in adult patients undergoing cardiac surgery remains inaccurate and should be further improved. Therefore we aimed to identify risk factors that are predictive of mortality, stroke, renal failure, and/or length of stay after adult cardiac surgery in contemporary practice.

Methods

We searched the Medline database for English-language original contributions from January 2000 through December 2011 to identify pre-operative independent risk factors of one of the following outcomes after adult cardiac surgery: death, stroke, renal failure, and/or length of stay. Two investigators independently screened the studies. Inclusion criteria were: (i) the study described an adult cardiac patient population; (ii) the study was an original contribution; (iii) multivariable analyses were performed to identify independent predictors; (iv) ≥1 of the predefined outcomes was analyzed; (v) at least one variable was an independent predictor, or a variable was included in a risk model that was developed.

Results

The search yielded 5,768 studies. After the initial title screening a second screening of the full texts of 1,234 studies was performed. Ultimately, 844 studies were included in the systematic review. In these studies, we identified a large number of independent predictors of mortality, stroke, renal failure, and length of stay, which could be categorized in variables related to: disease pathology, planned surgical procedure, patient demographics, patient history, patient co-morbidities, patient status, blood values, urine values, medication use, and gene mutations. Many of these variables are frequently not considered as predictive of outcomes.

Conclusions

Risk estimates of mortality, stroke, renal failure, and length of stay may be improved by inclusion of additional (non-traditional) innovative risk factors. Current and future databases should consider collecting these variables.

INTRODUCTION

Predicting procedural mortality in adult cardiac surgery is critical for decision-making purposes particularly when there are different treatments options available, as well as for benchmarking and outcome evaluation both at institutional and surgeon level. Several prediction models have been developed with the main goal of estimating the risk of operative mortality for patients undergoing coronary artery bypass grafting (CABG), aortic valve replacement (AVR), or cardiac surgery in general.[1-4] Despite their usefulness, it remains challenging to develop a risk model that performs accurately across the spectrum of low-, intermediate-, and high-risk patients evaluated for cardiac surgery. Although the recently developed EuroSCORE II may be associated with improvements when compared to the original additive and logistic EuroSCOREs,[5] risk prediction remains a challenge in European patients.[6-8] The Society of Thoracic Surgeons (STS) score has shown to outperform the EuroSCORE,[9-11] but still a number of studies has demonstrated poor model performance in certain patient subgroups.[12-14] Especially in high-risk patients, risk models have been shown to be poorly calibrated and overpredict mortality.

The reasons for suboptimal model performance are multifactorial. While conventional cardiovascular risk factors (e.g. renal failure, diabetes) are considered for inclusion in a model, less obvious factors may be valuable as well. Many risk models are developed through standard statistical approaches not taking into account risk factor interactions or procedure-specific weightings.[15] A mismatch is frequently present between the model development patient cohort and the patient cohort that it is used for in practice; some patient subgroups are continuously underrepresented.

Considering these arguments, it is important to i) clarify the purpose of a model, ii) develop a model that is useful, and iii) define the limits of that usefulness. Any model should be based on the available literature and clinical intuition to define the appropriate dataset for model development.

The EACTS is establishing a quality improvement programme for adult cardiac surgery with an international database as an important component, aiming to bring forward an EACTS risk model. We performed a systematic review of the literature to identify which variables may need to be collected to be able to develop a better risk prediction model.

METHODS

Search Strategy

We systematically searched the Medline database for English-language original contributions from January 2000 through December 2011 to identify pre-operative independent risk factors of one of the following outcomes after adult cardiac surgery: death, stroke, renal failure, and/or length of stay. Our search entry consisted of *outcome* keywords: 'mortality' OR 'death' OR 'stroke' OR 'cerebrovascular event' OR 'renal failure' OR 'length of stay' OR 'LOS'; *subject* keywords: 'cardiac surgery' OR 'heart surgery' OR 'heart valve surgery' OR 'valve replacement' OR 'AVR' OR 'MVR' OR 'valve repair' OR 'MVP' OR 'coronary artery bypass grafting' OR 'CABG'; and *analysis* keywords: 'risk model' OR 'risk score' OR 'risk factor' OR 'independent' OR 'multivariate' OR 'multivariable' OR 'c-index' OR 'c-statistic' OR 'area under the curve' OR 'AUC'.

Study Inclusion

Two investigators (S.J.H. and R.L.J.O) independently screened the studies identified by the search. During the first round of screening all titles were judged for their relevance. Studies evaluating non-cardiac surgery, percutaneous or transcatheter therapies, or diagnostic modalities were excluded. Many risk models have been developed for coronary artery bypass surgery and/or valvular surgery, therefore to be homogeneous but also comprehensive, we excluded studies that focused on pediatrics, congenital cases, aortic arch or root surgery, or heart transplants. Studies that were inconclusive with respect to the performed procedures and reported outcomes of a non-defined group, for example "patients that underwent cardiac surgery", were included.

After identifying potentially relevant studies, the full-length articles were screened using the following criteria: (i) the study indeed described an adult cardiac patient population; (ii) the study was an original contribution; (iii) multivariable analyses were performed to identify independent predictors; (iv) the outcome of mortality, stroke, renal failure, and/or length of stay was assessed; and (v) at least one variable was an independent predictor, or a variable was included in a risk model that was developed.

Data Extraction

For each endpoint, independent predictors were extracted from the included studies. The terminology of predictors differed significantly among studies. For example, "aortic calcification" was also reported as "extend of atherosclerotic ascending aorta disease", "thoracic aorta total plaque-burden", or "severe atheromatous aortic disease". Risk factors were measured and reported according to different indexes; for example, renal func-

tion was indicated with serum creatinine, creatinine clearance, or estimated glomerular filtration rate. Such variations were merged into a single variable to avoid repetition.

RESULTS

The search yielded 5,768 results (Figure 1). After excluding non-relevant studies from an initial title screening a second screening of the full texts of 1,234 studies was performed. Another 351 studies were found to be irrelevant because the patient population did not meet the criteria, the endpoint used was not death, stroke, renal failure, or length of stay, or no independent predictors were identified. The full texts of 78 studies could not be retrieved so the abstracts were screened for their relevance. Ultimately, 844 studies were included in the systematic review.

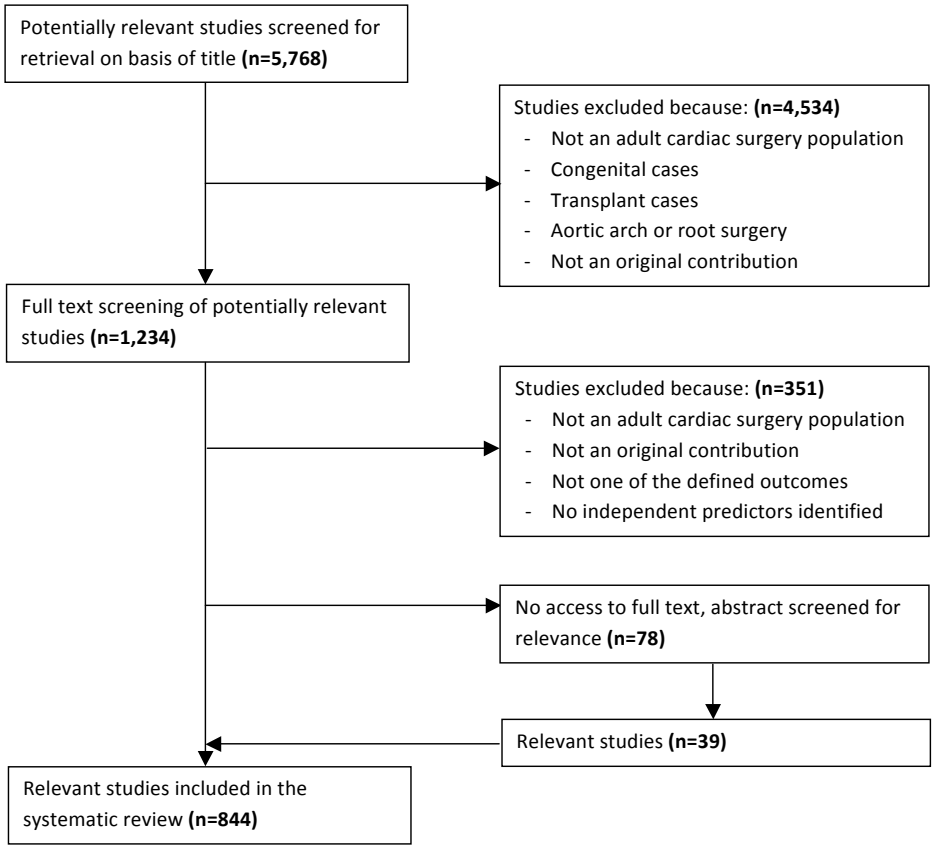

Figure 1. Flow Diagram: Systematic Inclusion of Studies

Table 1. Patient's Disease Pathology and Planned Surgical Procedure

Disease pathology	Planned surgical procedure
Number of coronary vessel disease	Coronary artery bypass grafting
Significant left main stenosis	Aortic valve replacement
Coronary artery disease complexity (e.g. SYNTAX score)	Aortic valve repair
Aortic valve stenosis	Aortic root surgery
Aortic valve regurgitation	Mitral valve replacement
Mitral valve stenosis	Mitral valve repair
Mitral valve regurgitation	Tricuspid valve replacement
Tricuspid valve regurgitation	Tricuspid valve repair
Persistent atrial fibrillation	Aortic surgery
Ascending aorta aneurysm	MAZE
Aortic arch aneurysm	

The diagnosed disease pathology and planned surgical procedure are essential elements in a risk model and always need to be documented (Table 1). The independent predictors of death, stroke, renal failure, and length of stay are listed in Tables 2-5. The predictors were categorized as patient demographics, patient history, patient co-morbidities, patient status, blood values, urine values, medication use, and gene mutations.

DISCUSSION

In this systematic review we screened 5,768 studies and included 844 studies in which we identified relevant independent predictors of death, stroke, renal failure, and length of stay after adult cardiac surgical procedures. This study was the first to identify systematically all predictors of adverse events after coronary artery bypass grafting and/or valvular surgery in adults. Many risk factors with a significant impact are frequently not considered when evaluating patients for major invasive procedures. Decision-making may be improved by taking into account these neglected yet predictive risk factors. Beside demographics (e.g. age, gender), disease complexity (e.g. coronary and/or valve lesions), and co-morbidities (e.g. renal failure), other factors such as medication intake and the patient's psychiatric, mental, and social-economic status have also been shown to have a predictive power.[16-17]

Over the last decade(s) there has been a growing interest in risk prediction models both for monitoring innovations and benchmarking outcomes as well as for clinical use to multidisciplinary shared-decision-making. The latter is especially true in an era of expanding multi-modality therapy for coronary artery and aortic valve disease when risk

prediction plays an important role to determine which patients would benefit most from surgery or interventional therapy.[18]

The inaccuracy of risk models may in part be due to the selection of variables.[18] As shown by previous studies, risk models are inconsistent in including variables and are missing several different yet important risk factors,[19-20] although until now it has been unclear which factors need to be considered. Furthermore, different definitions are used for some of the risk factors, resulting in a different weighting of that factor between models. Collection of the variables identified in this study may help to improve future risk models, and standardize risk factor definitions best suitable for inclusion.

A number of studies has identified genetic variations or mutations that carry an increased risk of adverse events after cardiac surgery. Indeed, collection of these variables in a large database could potentially provide insights into the understanding of the patient's risk, but it might be too optimistic to apply genetic profiling to a large international database. Costs of sequencing technologies are decreasing, but genetic profiling is still not widely used. It will be interesting to see whether genetic phenotyping might be more suitable to identify patients at higher risk of adverse events,[21] although little evidence is available at this time to use this technique for risk stratification in cardiac surgery. Some of the laboratory values or echocardiographic measures that have shown to be independent predictors may be too costly to collect. Quality of life assessments are time-consuming activities that will need to be performed by educated research nurses. Therefore, a model will always be lacking some variables that could potentially increase its performance.

The balance between the number of variables and model performance should be carefully considered when developing a risk model. Although many variables may be predictive (Tables 2-5), they cannot all be included because this will decrease the user-friendliness of the model.[22] Furthermore, a great number of variables will likely result in missing data that will have a negative impact on the accuracy of a newly developed risk model. On the other hand, ignoring some of these variables may produce a model with modest performance at best. It is recommended to exclude only variables with little impact on the predictive value of the model. Factors must be relatively present in the population, and enough adverse events must occur in a frequent manner to be able to have enough power for each risk factor to weight it in a multivariate model. Factors that are only present in a very small minority (<1%) of patients may not be relevant to collect, although their relative weight may be high. Ideally, the impact of the identified risk factors would be used to select which factors are more important to collect than others. However, to obtain an accurate estimate of the impact on the model, a broad range of risk factors need to be collected – including (non-)conventional factors – in a large database. Only then can

Table 2. Independent Predictors of Death

Demographics	Age; Gender; Race; Weight; Height; Body surface area; Geographic region (city, rural); Social economic status; Employment status (unemployed); Type of personality; Family history; Primary payer; Current smoker; Alcohol abuse
History	Pack-years smoking; Previous hospitalization for heart failure; Timing and number of previous PCI; Timing of congestive heart failure; Timing and location of previous MI*; Timing of dialysis; Timing of previous TIA/CVA; Timing of previous angina; History of hematological disorder/coagulopathy; Previous surgery for thrombosis; History of thyroid disease; Immune deficiency; Connective tissue disease; Pathological weight-loss; Pacemaker implantation; Number and type of reoperations
Co-morbidities	Diabetes; Metabolic syndrome; Cerebrovascular disease; Neurologic disorder; Depression; Anxiety; Psychoses; Carotid artery disease; Peripheral vascular disease; (Severity of) Atherosclerotic aortic disease; Atrial fibrillation; Type of arrhythmia; Hypertension; Pulmonary function/disease (e.g. COPD); Pulmonary hypertension; Renal function/failure; Liver function/disease; Malignancy Peptic ulcer disease
Status	Frailty; Energy level; Problems with self-care; Non-ambulatory state; Mental component score (SF-36); Physical component score (SF-36); Health status (EQ-5D); CCS classification; NYHA classification; LVEF; LV end-systolic diameter/volume; LV hypertrophy; LV end-diastolic pressure/diameter; Restrictive LV filling; LV posterior wall thickness; LV mass index; Lack of contractile reserve; Left atrial diameter; Small annulus; RV end-diastolic area; Right atrial pressure; Cardiothoracic ratio; Heart rate; Conduction defect; Corrected QT interval; Amount of ST-segment depression; Pre-operative ICU stay; On intubation/ventilation; Sepsis; Active endocarditis; Vegetation size (endocarditis); Prosthetic valve endocarditis; Staphylococcus endocarditis infection; Pulmonary edema; Ventilator-associated pneumonia; Multi organ failure; Ventricular assist device; Resuscitation; Postinfarct septal rupture; Unstable/Shock; Intra-aortic balloon pump; Urgency of surgery; ASA score; Pulse pressure
Blood values	Hemoglobin; Hematocrit; Homocysteine; Creatinine; HbA1c; Glucose; CRP; BNP; NT-proBNP; Interleukin 6; Endotoxin core antibody; Sodium; Magnesium; Protein; Albumin; Bilirubin; ASAT; Uric acid level; CK-MB; High-sensitive Troponin T; Troponin T; Troponin I; Lactate dehydrogenase; INR group; PTT; Antithrombin 3; HPF4 antibodies; Thrombocytes; Lymphocyte; Neutrophil; Total cholesterol; Non-HDL cholesterol; Cholesterol esters; Triglycerides
Urine values	Proteinuria
Medications	Aspirin; Warfarin or Coumadin; Other anticoagulant; Thrombolysis; Nitroglycerin; Statin; Beta-blocker; Catecholamine; Digoxin; Digitalis; Antidepressant (SSRI); Inotropic support; Immunosuppressive therapy
Gene mutations	C677T mutation in MTHFR gene; VEGF +405 GG; rs10116277 (2 allele) -- Chromosome 9p21; rs1042579 recessive

*Inferior/anterior myocardial infarction. ACE, angiotensin-converting enzyme; ASA, American Society of Anaesthesiologists; BNP, brain natriuretic peptide; CCS, Canadian Cardiovascular Society; CK-MB, creatine kinase myocardial band; COPD, chronic obstructive pulmonary disease; CRP, c-reactive protein; CVA, cerebrovascular accident; HDL, high density lipoprotein; HPF4, heparin-platelet factor 4; INR, international normalized ratio; MI, myocardial infarction; NT-proBNP, N-terminal-pro-brain natriuretic peptide; NYHA, New York Heart Association; PTT, partial thromboplastin time; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack.

Table 3. Independent Predictors of Stroke

Demographics	**Status**
Age	Left ventricular ejection fraction
Gender	Active infection
Race	Active endocarditis
Body surface area	Intra-aortic balloon pump
Current smoker	Unstable/Shock
History	Urgency of surgery
Timing of smoking	Pulse pressure
Timing of previous TIA/CVA	**Blood**
Timing of previous MI	Hemoglobin
Previous deep vein thrombosis	Creatinine
Number of reoperations	INR group
Dialysis	**Medications**
Co-morbidities	Aspirin
Diabetes	Statin
Cerebrovascular disease	ACE inhibitor
Neurologic status (e.g. deficit, dementia)	Beta-blocker
Carotid artery disease	Inotropic support
Peripheral vascular disease	**Gene mutations**
(Severity of) Atherosclerotic aortic disease	Interleukin 6 (−174G/C)
Atrial fibrillation	CRP 3'UTR1846C/T
Hypertension	
Hypercholesterolemia/lipidemia	
Renal function/failure	
Pulmonary hypertension	
Left ventricular hypertrophy	

ACE, angiotensin-converting enzyme; CVA, cerebrovascular accident; INR, international normalized ratio; MI, myocardial infarction; TIA, transient ischemic attack.

unnecessary risk factors be excluded. Collection of these factors will furthermore identify specific factors with international variation in prevalence or dynamic effect weights, which might result in different or a changing impact of factors on short- and/or long-term risk.[23]

It is unrealistic to collect for each patient the hundreds of variables that were identified in this study. It might be appropriate to start data collection with a small selection of centers as a feasibility project. This helps to determine the relative impact of certain variables and whether it is necessary and possible to collect these on a larger scale. Nevertheless, even in a feasibility design there are variables that may need to be prioritized over others. This study provides a framework for future model development, from which certain variables can be chosen depending on the prevalence of a risk factor, its relative

Table 4. Independent Predictors of Renal Failure

Demographics	Age; Gender; Race; Height; Weight; Body surface area
History	Timing of previous MI; Timing of recent cardiac catheterization; Timing of previous PCI; Dialysis; Congestive heart failure; Number or reoperations
Co-morbidities	Diabetes; Metabolic syndrome; Cerebrovascular disease; Carotid artery disease; Peripheral vascular disease; Atrial fibrillation; Hypertension; Renal function/failure; Pulmonary disease (e.g. COPD); Pulmonary hypertension; Charlson comorbidity index
Status	CCS classification; NYHA classification; Left ventricular ejection fraction; Sepsis; Active endocarditis; Intra-aortic balloon pump; Unstable/Shock; Urgency of surgery; ASA physical status
Blood values	Hemoglobin; Hematocrit; Creatinine; Platelet count; HbA1c; Hyperuricemia; Urea nitrogen; Bicarbonate; Sodium; Albumin; Bilirubin
Urine values	Albumin to creatinine ratio; Proteinuria
Medications	Statin; Calcium channel blocker; ACE inhibitor; Renin-angiotensin system inhibitor; Diuretic; Immunosuppressive therapy
Gene mutations	Catechol-O-methyltransferase LL

ACE, angiotensin-converting enzyme; ASA, American Society of Anaesthesiologists; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

impact, the patient population, the type of model (e.g. short-or long-term), the endpoints for which the model is developed, and the cost and resources available.

Risk models that have been developed on a cohort of patients undergoing a specific procedures may have limited value when applied to other population groups, as the impact of any one variable can have a very different weighting when applied to a cohort of patients undergoing another procedure. This may also be one of the reasons why risk models fail to predict accurately outcomes of low- to high-risk patient cohorts. This is clearly evident when examining the predictive power of the original EuroSCORE. It was developed on relatively low-risk patients undergoing CABG[24] but subsequently has been widely used with limited value for high-risk AVR, probably because such patients were hardly represented in the EuroSCORE database.

The EuroSCORE II was developed with 22381 patients of which 46.7% and 46.3% underwent isolated CABG and valve procedures, respectively.[5] However, recent evidence suggests that this more balanced inclusion of procedures was at the expense of decreased model performance in isolated CABG procedures.[8] Although generic risk models are useful in describing the risk profile of large patient populations included in randomised clinical trials or registries, procedure-specific models for CABG, AVR, and mitral valve surgery are advocated to increase risk prediction for individual patients. Clearly some of the risk factors we identified will more likely be included in a CABG risk model while

Table 5. Independent Predictors of Length of Stay

Demographics	Age; Gender; Race; Height; Weight; Body surface area; Geographic region (e.g. rural area); Social status
History	Previous TIA/CVA; Previous embolism; Timing of MI; Timing of PCI; (Duration of preceding) Hypertension; Previous arrhythmia treatment; Dialysis; Previous endocarditis; Congestive heart failure; Number of reoperations
Co-morbidities	Diabetes; Cerebrovascular disease; Peripheral vascular disease; Atherosclerotic aortic disease; Atrial fibrillation; Arrhythmia; Hypertension; Pulmonary function/disease (e.g. COPD); Pulmonary hypertension; Renal function/failure; Post-traumatic stress disorder; Depression; Liver function/failure; Malignancy; Dyslipidemia/hypercholesterolemia; Hyperglycemia
Status	SF-36 quality of life; CCS classification; NYHA classification; Left ventricular ejection fraction; Diastolic dysfunction; Right ventricular end-systolic diameter; Cardiothoracic ratio; Frailty; Immunosuppressive therapy; Rheumatic fever; Active infection; Active endocarditis; Large endocarditis vegetation (15mm); Unstable/Shock; Intra-aortic balloon pump; Urgency of surgery
Blood values	Hemoglobin; NT-pro-BNP; BNP; Creatinine
Medications	Beta-blocker; Nonaspirin platelet inhibitor; Inotropic support
Gene mutations	Il-8-251AA; Catechol-O-methyltrasferase LL

BNP, brain natriuretic peptide; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; MI, myocardial infarction; NT-proBNP, N-terminal-pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

others are more specific for an AVR model, such as the SYNTAX score or prosthetic valve endocarditis, respectively. The predictive power of some factors remains unclear when evaluating a cohort of patients undergoing a specific procedure, which is why there is a need to collect these factors in a generic database. This will furthermore provide the opportunity to examine whether useful generic models with procedure-related interaction terms can be constructed or whether only procedure-specific models are required for accurate risk prediction.

One major limitation of the widely used European risk scores remains that they have been developed to predict operative mortality although this is not the only outcome of interest to either patients, health care systems or policy makers. Many variables predictive of death will also be significant for other outcomes including renal failure, stroke, and length of stay. However, the associated odds ratios might be different for specific outcomes. For example, in the STS model for isolated valve surgery the OR of active infectious endocarditis for mortality is 1.95 (95% CI 1.68-2.27) but 2.79 (95% CI 2.51-3.09) for prolonged length of stay.[4] One of the goals of the forthcoming EACTS risk model will be to develop a model able to predict accurately multiple outcomes using outcome-specific ORs, similar to the STS risk model.

Although risk models can be improved, random events will always occur and a prediction model can therefore never be perfect. Thus, clinical guidelines recommend that clinical decision-making related to interventional and surgical interventions should be performed by a multidisciplinary Heart Team that consists of at least an interventional cardiologist and cardiovascular surgeon to interpret and weight risk models and additional information to come up with the most appropriate treatment recommendation for the individual patient.[25]

Limitations

The focus of this study was adult patients undergoing coronary artery bypass grafting and/or valve surgery, because the available surgical risk models have predominantly been developed for these populations. Although there may indeed be significant overlap, the identified independent risk factors may not be applicable to other surgeries such as on the aortic root or aorta, congenital cases, or heart transplantations.

Conclusions

This systematic review identified a significant number of independent predictors of adverse outcomes after adult coronary and valvular procedures, many of which are frequently not considered. These variables will be collected in a dedicated European database, and used for the development of the forthcoming EACTS risk model. However, the clinical value of these risk factors needs to be weight against the cost and effort of collecting them.

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CHAPTER 18

Commentary to "Survival Prediction Models for Coronary Intervention: Strategic Decision Support"

Kappetein AP, Osnabrugge RL

Ann Thorac Surg. 2014;97:528-9.

Risk scores, such as The Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM) and the European System of Cardiac Operative Risk Evaluation (EuroSCORE), are important tools to better understand which variables play a role in predicting hospital outcome in patients undergoing cardiac surgery. However, these scores are inadequate to predict long-term outcome and unable to assess the negative consequences of a procedure. Risk-benefit analysis is particularly important when several treatment options are available. Myocardial revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) is appropriate when the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and quality of life), exceed the expected negative aspects of the procedure. For multivessel disease, CABG is associated with a lower rate of major adverse cardiac and cerebrovascular events, mainly driven by a lower repeat revascularization rate and in subsets even with a lower mortality. Conversely, surgery is associated with post-operative cognitive impairment and higher stroke rate, longer hospitalization, and post-operative pain. The tradeoff that physicians and patients face in choosing between the benefits of CABG versus PCI (or medical treatment) requires complex risk-benefit modeling.

The decision support tool as presented by Raza and colleagues[1] is a valuable instrument as it predicts prognosis after PCI and CABG. A model was constructed to predict 5-year outcome for CABG versus PCI with drug-eluting stents and 10-year outcome of CABG versus PCI with bare metal stents. The reliability of these models depends on the variables that were collected in the past and that can be used to construct a model that is reliable in the current era.[2] The extensiveness of coronary artery disease is a major predictor for outcome among patients treated with PCI, and the categorization of patients into one-, two-, or three-vessel disease is insufficient. There are patients with three-vessel disease with discrete lesions and easy to treat with PCI (type A lesions); and there are also patients with chronic total occlusions, excessive tortuosity, or a length of more than 2 cm (type C lesions) whose outcome for PCI is less optimal. The Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) score takes these factors into account and is a major predictor for outcome with PCI.[3] Cardiologists are treating increasingly complex lesions, and a description of the coronary anatomy is crucial to account for these differences in practice. Raza and coworkers[1] provide an example how their model can be used to predict long-term outcome with PCI or CABG in patients with left main stenosis. That should, however, be interpreted with caution. A midshaft left main stenosis is different from one with bifurcation or associated three-vessel disease. The SYNTAX study showed that even patients with diabetes mellitus and left main stenosis with a low SYNTAX score did as least as good with PCI as with CABG whereas patients with a higher SYNTAX score and left main stenosis were better off with surgery.[2] If the results of the SYNTAX study are repeated in the EXCEL (Evaluation

of XIENCE PRIME Everolimus Eluting Stent System or XIENCE V EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (PCI versus CABG in left main stenosis and a SYNTAX score less than 33), it is likely that the recommendation for PCI in patients with left main disease will be upgraded.

The recently published SYNTAX score II combines anatomic factors as well as comorbidities to predict long-term mortality associated complex coronary artery disease.[4]

These models help physicians to make recommendations, but a heart team approach to individualize treatment is needed to ensure that every patient receives the optimal therapy. The paper by Raza and colleagues adds to the armamentarium of the heart teams so as to not only focus on hospital mortality but also on the long-term results as well.[1] It is hoped that future models will also be able to predict outcomes other than just mortality.

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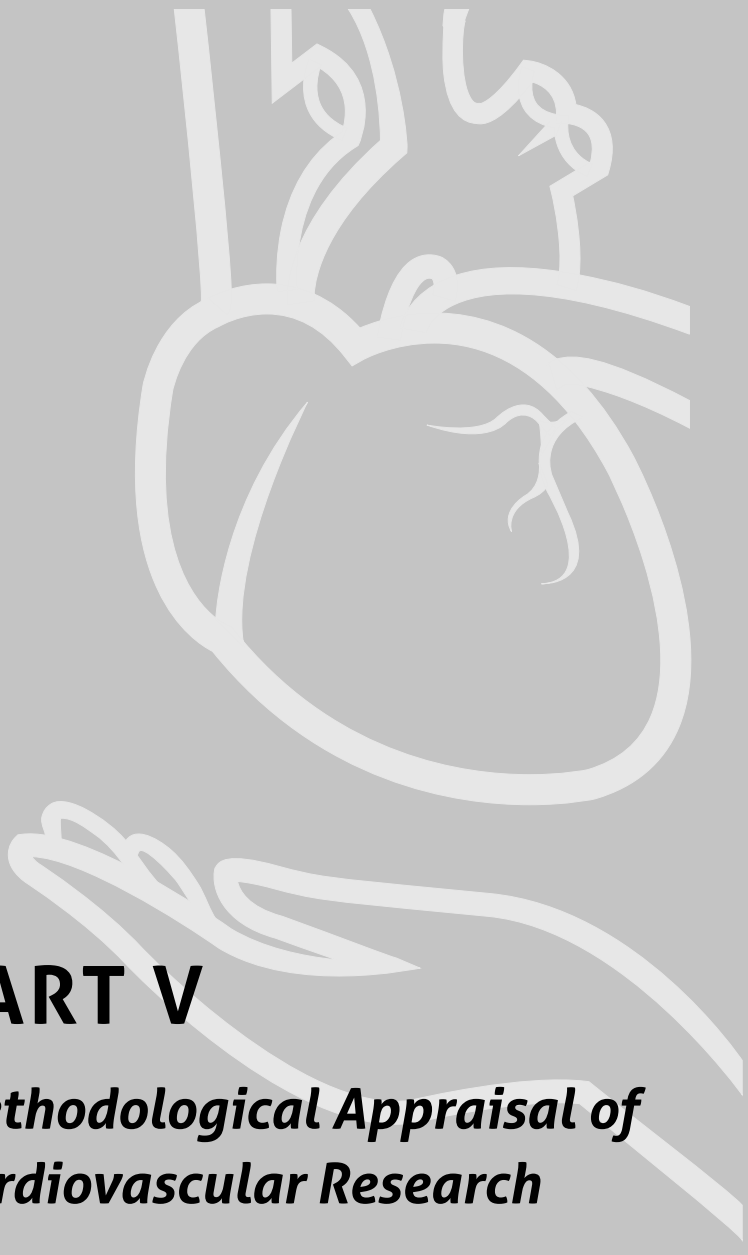

PART V

Methodological Appraisal of Cardiovascular Research

CHAPTER 19

Carriage of Reduced-Function CYP2C19 Allele among Patients treated with Clopidogrel

Osnabrugge RL, Kappetein AP, Janssens AC.

JAMA. 2011;305:467-8.

TO THE EDITOR:

The meta-analysis of Mega et al. shows that among patients treated with clopidogrel for percutaneous coronary intervention, carriage of 1 reduced function CYP2C19 allele is associated with an increased risk of major adverse cardiovascular events (hazard ratio (HR), 1.55; 95% confidence interval (CI), 1.11-2.17).[1] Two methodological issues hamper the interpretation of the results.

First, the authors used an inappropriate strategy to reduce the substantial heterogeneity in their meta-analysis (I^2 = 73%). They removed the two studies that caused heterogeneity (AFIJI[2] and FAST-MI[3]) and found that the summary HR remained significant (HR, 1.42; 95% CI, 1.19-1.69; I^2 = 0%). Removing the AFIJI study seems justified since the mean age, smoking status and sex of the patients were substantially different compared to the other studies.[2] For example, the mean age of patients in the AFIJI study was 40.1 years, whereas the overall mean age across all studies was 64.2 years. Yet, excluding the FAST-MI study cannot be justified. The study is very comparable and should not be removed for the mere fact of introducing heterogeneity.[3] We repeated the meta-analysis excluding AFIJI only and found a lower and borderline significant summary HR of 1.34 (95% CI, 1.01-1.78; I^2 = 62%).

Second, the authors did not report on the assessment of potential bias that may have impacted their results. It is known that meta-analyses are subject to bias including first-study, selective reporting and publication bias.[4, 5] The presence of bias is examined using several plots and tests that are available. One indication for the presence of publication bias is a difference in effects between the large and small studies.[5] We compared the summary HR of the four smallest and four largest studies and found a summary HR of 2.09 (95% CI, 1.29-3.40; I^2 = 0%) in the smallest studies and a HR of 1.15 (95% CI, 0.84-1.59; I^2 = 75%) in the largest studies. The absence of a genetic association in the larger studies suggests that the statistically significant HR in the overall meta-analysis may be due to publication bias.

Our analyses raise questions about the presence of an association between CYP2C19 and the risk of adverse cardiovascular events in users of clopidogrel. More studies are needed to clarify the persisting heterogeneity in results.

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CHAPTER 20

A Systematic Review and Critical Assessment of 11 discordant Meta-analyses on Reduced-Function CYP2C19 Genotype and Risk of Adverse Clinical Outcomes in Clopidogrel Users

Osnabrugge RL, Head SJ, Zijlstra F, Ten Berg JM, Hunink MG, Kappetein AP, Janssens AC.

Genet Med. 2014; In Press.

ABSTRACT

We systematically investigated how 11 overlapping meta-analyses on the association between *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel could yield contradictory outcomes. The results of the meta-analyses differed because more recent meta-analyses included more primary studies and some had not included conference abstracts. Conclusions differed because between-study heterogeneity and publication bias were handled differently across meta-analyses. All meta-analyses on the clinical endpoint observed significant heterogeneity and several reported evidence for publication bias, but only one out of eight statistically significant meta-analyses concluded that therefore the association was unproven and one other refrained from quantifying a pooled estimate because of heterogeneity. For the endpoint stent thrombosis, all meta-analyses reported statistically significant associations with *CYP2C19* loss-of-function alleles with no statistically significant evidence for heterogeneity, but only three had investigated publication bias and also found evidence for it. One study therefore concluded there was no evidence for an association, and one other doubted the association because of a high level of heterogeneity. In summary, meta-analyses on the association between *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel differed widely with regard to assessment and interpretation of heterogeneity and publication bias. The substantial heterogeneity and publication bias implies that personalized antiplatelet management based on genotyping is not supported by the currently available evidence.

INTRODUCTION

Clopidogrel, in combination with aspirin, is a standard treatment for patients with acute coronary syndrome (ACS) and is one of the top-selling drugs in the world.[1, 2] However, there is substantial inter-individual variability in response. Polymorphisms of the Cytochrome P450 (CYP) gene have been identified as a potential risk factor for non-response.[3] This gene plays a central role in drug metabolising processes in the liver and clopidogrel makes use of these processes to transform into an active metabolite capable of inhibiting platelet aggregation. Identification of *CYP2C19* polymorphisms could lead to personalized treatment based on genotype in patients with ACS and therefore the US Food and Drug Administration recommends *CYP2C19* genotyping for individualized antiplatelet management.[4]

The association between *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel has been studied extensively and several meta-analyses have summarized the results of those studies.[5-8] Systematic reviews and meta-analyses are often considered the highest level of evidence,[9-11] and their popularity in the cardiovascular field increased almost 13 times as fast as the increase in number of published randomized clinical trials (RCT).[12] However, the interpretation of meta-analyses is confusing when the conclusions of overlapping meta-analyses are discordant. Some meta-analyses on *CYP2C19* loss-of-function and clinical efficacy of clopidogrel conclude that the association is proven,[7, 8] whereas others conclude the opposite.[5, 6]

Our objective was to systematically evaluate the discordant evidence for the association between *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel through a critical methodological appraisal of published meta-analyses.

MATERIALS AND METHODS

Our review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement,[13] and we consulted the Cochrane Handbook for Systematic Reviews of Interventions for methodological aspects of meta-analyses.[14]

Literature Search and Study Selection

A MEDLINE search was performed in August 2013 using a combination of search terms: (clopidogrel OR Plavix OR Iscover OR thienop* OR P2Y12) AND (cytochrome OR cyp OR polymorph* OR genetic*) AND (review OR meta-analysis). The Cochrane Database of Systematic Reviews, The Web of Knowledge, EMBASE and reference lists of retrieved systematic reviews were inspected for additional studies.

Two reviewers (RO and SH) independently assessed all titles and abstracts for eligibility, and examined all full-text articles to find meta-analyses of *CYP2C19* polymorphisms and clinical outcomes in clopidogrel users. Disagreements were resolved by discussion.

Data Extraction

General, clinical and methodological characteristics of each meta-analysis were extracted from for each meta-analysis, independently by two researchers (RO and ACJWJ). General characteristics consisted of first author, year of publication, and the date (month/year) when the authors had performed their systematic search. Clinical characteristics comprised the population and outcome definitions, and methodological characteristics were the eligibility of abstracts, the number of included studies, the method of assessment of primary study quality, details of the statistical analysis (random/fixed effects meta-analysis), and the main results with confidence intervals. The literal conclusion of the authors about the presence of an association was documented from the abstract and categorized into present or absent. When the literal conclusion was unclear or not reported in the abstract, the wording was obtained from the discussion in the main text.

We examined whether and how the meta-analyses had addressed between-study heterogeneity and publication bias. These methodological characteristics are important for grading the quality of the evidence in the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) and Assessment of multiple systematic reviews (AMSTAR) tools.[15-17] Heterogeneity is an apparent difference between the results of the primary studies,[13, 14] and may be present when study populations, interventions, outcomes, or methodologies differ across the studies. Heterogeneity is generally quantified by the I^2 or Cochran's Q-statistic. Values of <25% suggest little heterogeneity, 25–50% suggests moderate heterogeneity, and >50% means large heterogeneity.[18] We extracted these metrics, and documented the methods that the authors had used to examine differences in the results. To evaluate heterogeneity, primary study characteristics were extracted, which included study design, follow-up duration, patient characteristics and outcome definitions. Publication bias is the tendency by investigators, reviewers and editors to submit or accept manuscripts for publication based on the direction or strength of the study findings.[19] Tests that assess publication bias include funnel plots, Harbord-Egger tests, and trim and fill analyses.[20-22] We extracted the specific methods that the authors used as well as their conclusions on the presence of publication bias.

RESULTS

Search Results

The MEDLINE search yielded 347 articles from which 11 meta-analyses on the association between *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel were identified. The searches in other databases and reference lists yielded no additional meta-analyses. The 11 meta-analyses included a total of 30 primary studies, but not all studies were included in all meta-analyses.

Meta-Analyses Characteristics

The 11 meta-analyses were published within a timeframe of 24 months, and their literature searches were performed between October 2009 and October 2011. All articles presented separate analyses for composite clinical endpoints and stent thrombosis (ST). The definitions of the composite clinical endpoint varied across meta-analyses, but generally included death, myocardial infarction (MI) and stroke (Table 1). ST was typically defined according to the academic research consortium definitions.[23] Five meta-analyses used a checklist to assess the quality of the primary studies,[5, 7, 8, 24, 25] three meta-analyses used their own approach,[6, 26, 27] or did not check the quality.[28-30] The Newcastle-Ottawa scale is a formal quality scoring list,[31] whereas the Strengthening the reporting of observational studies in epidemiology (STROBE),[32] and its genetic extension STrengthening the REporting of Genetic Association studies (STREGA) also serve as reporting guidelines.[33] However, all three checklists comprise methodological aspects of observational studies including patient selection, outcome assessment and adequacy of follow-up.

The total number of included studies ranged from 7 to 27 for the clinical endpoint and from 4 to 14 for ST (Table 1, Supplementary Table 1-2, Appendix). As expected, more recent meta-analyses generally included more primary studies. The percentage of all studies that were included in the meta-analysis, calculated as the percentage of all available studies at the date of the study selection, ranged from 25% to 90% for the clinical endpoint and from 9 to 82% for ST (Supplementary Table 1-2, Appendix). Five meta-analyses did not include conference abstracts,[5, 25, 28-30] and all but one of the meta-analyses left out data from one or more full articles that were included in other meta-analyses (Supplementary Table 1, Appendix).[34-41] For example, the post-hoc genetic analysis of the ACTIVE-A trial was included in only two of the seven meta-analyses that did their literature searches after the publication of the trial.[6, 24] and one meta-analysis had limited the inclusion to only primary studies with a follow-up time of 6-12 months.[30]

Table 1. Characteristics of included Meta-Analyses, sorted by Publication Date

First author[ref]	Publication date	Search date	Definitions		Include abstracts	N studies		Quality check of primary studies
			Clinical endpoint	Stent thrombosis		Clinical endpoint	ST	
Hulot[7]	July 2010	Oct 2009	MACE: death, MI, stroke, urgent revascularization	Definite or probable according to ARC	Yes	10	4	Newcastle-Ottawa
Jin[28]	Sept 2010	Dec 2009	Clinical adverse events	Not defined	No*	8	5	Not reported
Mega[8]	Oct 2010	Aug 2010	CV-death, MI, stroke	Definite or probable according to ARC	Yes	9	6	STROBE
Sofi[29]	June 2011	Jan 2010	MACE: death, MI, stroke, unstable AP, ST, recurrent ischemia	Not defined	Yes	7	4	Not reported
Zabalza[25]	June 2011	Oct 2010	MACE: CV-death, MI, stroke, unstable AP, recurrent ischemia	Definite or probable according to ARC	No	11	7	STREGA
Liu[24]	July 2011	May 2011	MACE (not defined)	Not defined	Yes	18	9	Newcastle-Ottawa
Bauer[5]	Aug 2011	Dec 2010	MACE: death, MI, stroke	Definite: according to ARC Probable: only if reported with definite as a composite outcome. Possible: not considered.	No	12	9	Newcastle-Ottawa
Holmes[6]	Dec 2011	Oct 2011	Death from any cause, CHD, stroke, ST, revascularization, hospitalization for ACS	Not defined	Yes*	26	14	Own criteria, e.g., on outcome ascertainment, blinding to case status when ascertaining genotype and source of funding.
Jang[26]	May 2012	Sept 2011	Adverse clinical outcomes: death, MI, stroke, ST	Definite or probable according to ARC	Yes	16	10	Own criteria
Singh[27]	June 2012	May 2011	MACE (not defined), CV-death, MI, ST, stroke, major bleeding.	Definite or probable	Yes*	14	6	Own criteria, e.g., on concealment of randomization and completeness of follow-up
Yamaguchi[30]	July 2012	Oct 2011	CV events: death, MI, stroke, ST, revascularization	Not defined	No*	7	5	Not reported

Abbreviations: ACS, acute coronary syndrome; AP, angina pectoris; ARC, academic research consortium[23]; CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis; STREGA, Strengthening the Reporting of Genetic Association; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.
* The authors did not explicitly report the in/exclusion of abstracts, but this was inferred from the included studies.

Primary Study Characteristics

The characteristics of the 30 primary studies varied (Supplementary Table 3, Appendix). Follow-up duration ranged from 1 to 43 months and there were 23 cohort studies and 7 post-hoc analyses of randomized trials. The mean age ranged from 60 to 70 in most studies, with the exception of one study that involved patients with a mean age of 40 years old.[42] The percentage of patients that had undergone percutaneous coronary intervention (PCI) varied from 0% to 100%, and the proportion of smokers ranged from 8% to 56%, with three studies including more than 50% smokers.[42-44]

All 30 studies addressed clinical endpoints, and 17 also investigated ST. The definition of the composite clinical outcome and the event rates varied between primary studies. MI was most commonly included in the composite clinical endpoint (24 studies), followed by cardiovascular death (18 studies), stroke (17 studies), and all-cause death (10 studies).

Outcomes and Conclusions of the Meta-Analyses

Eight out of 11 meta-analyses on clinical endpoints reported a statistically significant association (Table 2, Supplementary Table 4, Appendix).[6-8, 24, 26-29] Mean effect sizes of the significant association (random effects models) ranged from 1.26 to 1.96. Five of these eight concluded that there was an association between *CYP2C19* loss-of-function alleles and the clinical endpoint,[24, 26-29] two inferred that there was a possible association,[7, 8] while one concluded that the association was not proven because of publication bias (Table 2, Supplementary Table 4, Appendix).[6] The remaining three meta-analyses found no statistically significant pooled effect,[5, 25] or did not pool the data because of between-study heterogeneity.[30] Of the four meta-analyses that concluded absence of association, three were among the five most recently published.[5, 6, 30]

For ST, all 11 meta-analyses reported a statistically significant association with *CYP2C19* loss-of-function alleles.[5-8, 24-30] Mean effect sizes (fixed effects models) ranged from 1.77 to 3.82. One meta-analysis concluded that there was a possible association,[6] and one other meta-analysis observed the presence of heterogeneity and publication bias, and downgraded the evidence (Table 2, Supplementary Table 4, Appendix).[5]

Heterogeneity

Heterogeneity assessment of each meta-analysis is presented in Table 3. All meta-analyses reported significant heterogeneity between the primary studies for the clinical endpoints, but they handled and interpreted the presence of heterogeneity in different ways. Six meta-analyses reduced heterogeneity by excluding one or more studies,[5, 8, 24-26, 29] and four of these found that the resulting pooled effect estimate remained unchanged.[5, 8, 24, 26] Five meta-analyses performed stratified meta-analyses by

Table 2. Main Outcomes for Clinical Endpoints and Stent Thrombosis

First author[ref]	Publication date	Main result* (95% CI)	Statistical significance	Heterogeneity	Bias	Conclusion about the presence of association
Clinical endpoint						
Hulot[7]	July 2010	1.45 (1.12-1.89)	Yes	Yes	No	Possible
Jin[28]	Sept 2010	1.46 (1.01-2.13)	Yes	Yes	NR	Yes
Mega[8]	Oct 2010	1.57 (1.13-2.16)	Yes	Yes	NR	Possible
Sofi[29]	June 2011	1.96 (1.14-3.37)	Yes	Yes	Yes	Yes
Zabalza[25]	June 2011	1.23 (0.97-1.55)	No	Yes	Yes	No
Liu[24]	July 2011	1.26 (1.06-1.50)	Yes	Yes	Yes	Yes
Bauer[5]	Aug 2011	1.11 (0.89-1.39)	No	Yes	Yes	No
Holmes[6]	Dec 2011	1.34 (1.15-1.56)	Yes	Yes	Yes	No
Jang[26]	May 2012	1.42 (1.13-1.78)	Yes	Yes	Yes	Yes
Singh[27]	June 2012	1.28 (1.07-1.55)	Yes	Yes	No	Yes
Yamaguchi[30]	July 2012	Not performed	NA	Yes	NR	No
Stent thrombosis						
Hulot[7]	July 2010	3.45 (2.13-5.57)	Yes	NR	Yes	Yes
Jin[28]	Sept 2010	3.81 (2.27-6.40) (F)	Yes	No	NR	Yes
Mega[8]	Oct 2010	2.81 (1.81-4.37)	Yes	No	NR	Yes
Sofi[29]	June 2011	3.82 (2.23-6.54) (F)	Yes	No	NR	Yes
Zabalza[25]	June 2011	2.24 (1.52-3.30)	Yes	No	NR	Yes
Liu[24]	July 2011	2.58 (1.77-3.77)	Yes	NR	NR	Yes
Bauer[5]	Aug 2011	1.77 (1.31-2.40)	Yes	Yes	Yes	No
Holmes[6]	Dec 2011	1.88 (1.46-2.41)	Yes	NR	NR	Possible
Jang[26]	May 2012	2.41 (1.76-3.30) (F)	Yes	No	NR	Yes
Singh[27]	June 2012	2.41 (1.70-3.41) (F)	Yes	No	Possible	Yes
Yamaguchi[30]	July 2012	2.65 (1.46-4.84) (F)	Yes	NR	NR	Yes

Abbreviations: CI, confidence interval; F, fixed-effects model; ST, stent thrombosis; LOF, loss-of-function; MACE, major adverse cardiovascular event; NA, not applicable; NR, not reported.
Authors' descriptions of their conclusions are shown in Supplementary Table 4.
* main results are based on random effects analysis, unless otherwise indicated, and represent odds ratios or hazard ratio according to each of the meta-analyses. Fixed effects analyses are reported in Supplementary Table 4.

study and population characteristics,[7, 8, 25, 26, 29] two performed meta-regression,[5,20] and one inspected primary study characteristics.[5] Higher sample size and poorer quality of the primary studies were associated with lower effect sizes,[7, 25] but other studies did not find an impact of study characteristics.[5, 6] For ST, four meta-analyses observed moderate heterogeneity, with I^2 ranging from 32% to 44%,[5, 6, 24, 27] but the degree of between-study heterogeneity was not statistically significant in any of the 11 meta-analyses. One meta-

Table 3. Analyses and Reporting of Between-Study Heterogeneity in the Meta-Analyses

First author[ref]	Publication date	Analyses	Clinical endpoint		Stent thrombosis	
			Statistic	Interpretation	Statistic	Interpretation
Hulot[7]	July 2010	• Q-statistic • Stratified meta-analysis by study characteristics	Q, p=0.003	Heterogeneity present. Exclusion of the studies with the lowest quality score or smallest sample size reduced heterogeneity and did not alter pooled effect.	Q, p=0.78	Not discussed
Jin[28]	Sept 2010	• I^2	I^2=70.4%, p=0.001	Heterogeneity present. In discussion: heterogeneity a potential problem when interpreting meta-analyses.	I^2=0%, p=0.86	No heterogeneity
Mega[8]	Oct 2010	• I^2, Q • Excluding studies to reduce heterogeneity • Stratified analyses by study characteristics	I^2=73%; Q=29.2, p<0.001	Heterogeneity present. Exclusion of two studies with the highest and lowest effect size reduced heterogeneity (I^2=0%) and did not alter pooled effect.	Q=4.4, p=0.49	No heterogeneity
Sofi[29]	June 2011	• I^2 • Excluding multiple studies to reduce heterogeneity • Stratified analyses by study characteristics	I^2=81%, p<0.0001	Heterogeneity present. Yet, fixed and random effects models gave similar results, and exclusion of three studies reduced heterogeneity (I^2=0%).	I^2=0%, p=0.90	No heterogeneity
Zabalza[25]	June 2011	• I^2 • Meta-regression on study characteristics • Stratified analyses by study characteristics • Excluding one study at a time	I^2=35.6%, p<0.001	Heterogeneity present. Stratified analysis showed heterogeneity in larger (I^2=15.2%, p=0.03), but not in smaller studies (I^2=2.9%, p=0.24).	I^2=8.8%, p=0.18	No heterogeneity
Liu[24]	July 2011	• I^2, Q • Excluding one study at a time	I^2=56%; Q=38.3, p=0.002	Heterogeneity present. Exclusion of studies did not alter pooled effect.	I^2=44%, p=0.08	Not discussed

Table 3. Analyses and Reporting of Between-Study Heterogeneity in the Meta-Analyses (*continued*)

First author[ref]	Publication date	Analyses	Clinical endpoint		Stent thrombosis	
			Statistic	Interpretation	Statistic	Interpretation
Bauer[5]	Aug 2011	• I^2, Q • Excluding multiple studies to reduce heterogeneity • Exploring study characteristics that caused heterogeneity	I^2=63.4% (95% CI: 31.9-80.3%), Q=30.1, p=0.002	Heterogeneity present. Exclusion of studies reduced heterogeneity (I^2=18.8%) and yielded non-significant effect estimate.	I^2=32.3 (95% CI: 0-68.8%), Q=11.8, p=0.16	Heterogeneity present. Exclusion of studies reduced heterogeneity (I^2=8.6%) and effect estimate remained significant.
Holmes[6]	Dec 2011	• I^2 • Meta-regression	I^2=60% (95% CI: 38-75%)	Heterogeneity present. Study characteristics did not modify association in meta-regression.	I^2=44% (95%CI: 0-70%)	Not discussed
Jang[26]	May 2012	• I^2, Q • Excluding one study at a time • Excluding multiple studies to reduce heterogeneity • Stratified analyses by study characteristics	I^2=61%; Q=38.9, p<0.001	Heterogeneity present. Exclusion of 5 studies reduced heterogeneity (I^2=0%) and did not alter pooled effect.	I^2=12%; Q=10.22, p=0.33	No heterogeneity
Singh[27]	June 2012	• I^2, Q	I^2=60.5%; Q=32.9, p=0.002	Heterogeneity present, and therefore random effects model was used.	I^2=31.5%; Q=7.3, p=0.20	No heterogeneity
Yamaguchi[30]	July 2012	• I^2, Q	I^2=56.5%; p=0.01	Heterogeneity present and therefore pooled OR not estimated	I^2=9.2%; p=0.24	Not discussed

Abbreviations: ACS, acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; LOF, loss-of-function; MACE, major adverse cardiovascular events; OR, odds ratio; ST, stent thrombosis.

analysis discussed that exclusion of studies reduced heterogeneity, but did not justify the exclusion on clinical grounds.[5]

Bias assessment

The assessment of publication bias is presented in Table 4. All but two meta-analyses investigated publication bias for clinical endpoints.[8, 28] Nine meta-analyses used fun-

Table 4. Analyses and Reporting of Publication Bias in the Meta-Analyses

First author[ref]	Publication date	Analyses	Conclusion	
			Clinical endpoint	Stent thrombosis
Hulot[7]	July 2010	• Funnel plot • Egger test	No publication bias	Publication bias present
Jin[28]	Sept 2010	Not reported	Not reported	Not reported
Mega[8]	Oct 2010	Not reported	Not reported	Not reported
Sofi[29]	June 2011	• Funnel plot	Funnel plot slightly asymmetric; publication bias could be present	Not reported
Zabalza[25]	June 2011	• Funnel plot • Stratified analysis by study size	Funnel plot slightly asymmetric; overestimation of effect size in smaller studies could be related to publication bias.	Not reported
Liu[24]	July 2011	• Funnel plot	Funnel plot showed a degree of asymmetry that may be consistent with small study bias	Not reported
Bauer[5]	Aug 2011	• Funnel plot • Harbord-Egger test • Re-analysis without first studies • Trim and fill analysis • Cumulative and recursive meta-analyses	Funnel plot showed a degree of asymmetry that may be consistent with small study or publication bias. No evidence for missing studies.	Funnel plot showed a degree of asymmetry that may be consistent with small study or publication bias. Evidence for first study bias and missing studies.
Holmes[6]	Dec 2011	• Funnel plot • Harbord-Egger test • Stratified analysis by study size • Trim and fill analysis	Publication bias present and had significant impact on the results	Not reported
Jang[26]	May 2012	• Funnel plot • Egger test • Trim and fill analysis	All analyses show evidence for publication bias	Not reported
Singh[27]	June 2012	• Funnel plots • Egger test	No publication bias	Possible publication bias
Yamaguchi[30]	July 2012	• Funnel plot	Not discussed	Not discussed

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; LOF, loss-of-function; MACE, major adverse cardiovascular events; OR, odds ratio; RR, relative risk; ST, stent thrombosis.

nel plots to explore publication bias,[5-7, 24-26, 29] of which five applied additional analyses such as (Harbord-)Egger tests, stratification analysis, and trim and fill analysis.[5-7, 26, 27] Six of the nine meta-analyses that assessed publication bias concluded that there was at least some evidence for bias due to selective missing studies,[5, 6, 24-26, 29] two did not find evidence for bias,[7, 27] and in one meta-analysis the results of the funnel plot were not discussed.[30] For ST, only 3 out 11 meta-analyses reported the analyses of publication bias and concluded that presence of bias could not be ruled out.[5, 7, 27] One of these meta-analyses concluded that the epidemiological credibility for an association of *CYP2C19* loss-of-function alleles with ST with was weak, due to publication bias.[5]

DISCUSSION

This review of 11 meta-analyses on the association between *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel shows that results and conclusions of 11 overlapping meta-analyses were discordant. Effect sizes differed because some meta-analyses did not include data from conference abstracts and more recent meta-analyses included more primary studies. Yet, conclusions predominantly differed because between-study heterogeneity and bias were handled differently across meta-analyses.

Overall, the meta-analyses consistently showed a larger effect of *CYP2C19* loss-of-function alleles on ST as compared to the effect on the clinical endpoint. ST is associated with higher risk of experiencing MI and death, both components of the composite clinical endpoint.[45] The absence of consistent association with clinical endpoints might indicate that the alleles have no impact on distant outcomes as MI and death, and that the significant effect of ST is diluted when combining the various endpoints. Liu and colleagues had performed meta-analyses on the separate clinical endpoints, such as bleeding complications, MI, stroke and death, and found that effect sizes ranged from 0.99 to 1.55, with the exception of 2.37 for stroke. None of these effect sizes were statistically significant and most analyses showed substantial between-study heterogeneity.[24] This suggests that *CYP2C19* impacts ST, and maybe stroke, but that its effect may not be strong enough to also influence the more distant outcomes.

All meta-analyses on the clinical endpoints observed substantial between-study heterogeneity. The heterogeneity was most likely explained by differences between study populations and primary outcome measures (Supplementary Table 3, Appendix). For example, the mean age of the participants in the study by Collet et al. was 40 years,[42] compared to 60 to 68 years in all other studies. In all studies, the percentage of smokers ranged from 8 to 56%, the percentage of men from 55 to 92%, and the percentage of

participants who underwent PCI from 0 to 100%. The effect of clopidogrel response should preferably be in a more homogenous subgroup, since the influence of age, gender, and smoking status on CYP enzyme activity cannot be neglected.[46-48] The study by Collet et al. had the highest effect size of all studies (5.4, 95% confidence interval 2.3-12.5), and its exclusion from meta-analyses would have been justified based on its incomparable study characteristics.[49] Also from a clinical perspective, exclusion of the study by Collet et al. is warranted: a decision about genotyping 60-70 year old individuals should not be affected by a three-fold higher effect size in young adults.

The substantial heterogeneity between the primary studies was handled differently across the meta-analyses. Several meta-analyses excluded studies with extreme effect sizes (outliers) one by one to reduce heterogeneity. The removal of studies for the mere fact of introducing heterogeneity is however unjustifiable, because, by definition, heterogeneity is introduced by the studies with the most extreme effects and never by studies that have effect sizes similar to the pooled estimate. Moreover, only very large studies with extreme effects may lead to a change in the pooled estimate after its exclusion. Exclusion of smaller studies easily reduces heterogeneity without changing the pooled effect. Yet, exclusion of studies should not be based a posteriori on the effect sizes, but a priori on the basis of patient or study characteristics, preferably by pre-specified subgroup-analysis that details and motivates the exclusion of specific studies.[14, 50, 51] The presence of substantial unexplained heterogeneity should be a major factor in the interpretation of the evidence and a good reason to refrain from drawing conclusions based on the quantitative results.[14]

Another factor that affected the interpretation of the relationship between *CYP2C19* variants and clinical efficacy of clopidogrel was the presence of bias. Meta-analyses are subject to various biases including small-study and publication bias.[13, 52] Small-study bias is present when the smaller studies show stronger effects than the larger studies, and publication bias might occur when studies with statistically significant results are more likely to be published than those with non-significant results.[22] For the clinical end point, 6 of 11 meta-analyses found evidence for publication bias, and the 3 meta-analyses that investigated publication bias for the ST end point found that the results were biased due to missing studies.[3, 5, 27] These bias checks suggest that the association of *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel is affected by missing studies, studies that would have shown smaller effects or even effects in the opposite direction.

Despite the substantial heterogeneity in the meta-analyses of the clinical endpoint and the suggestions of publication bias in both the clinical endpoint and ST, most meta-analyses did not seem to consider these data problems in their conclusions. Only 1 of the

11 meta-analyses on the clinical endpoint explicitly refrained from quantitative analysis because of heterogeneity,[30] one downgraded the statistically significant association to evidence of no association,[6] and two others phrased their conclusions of associations cautiously.[7, 8] Yet, 5 out of 8 meta-analyses that observed statistically significant effects concluded that the *CYP2C19* genotype was associated to the clinical endpoint despite the presence of substantial between-study heterogeneity.[24, 26-29] For ST, 8 out of 11 meta-analyses did not reported about the assessment of bias,[6, 8, 24-26, 28-30] whereas the 3 who did such assessment found evidence for publication bias. Inspections of heterogeneity and bias are integral parts of meta-analyses and their results should impact the conclusions of the quantitative analysis.[13, 15-17]

The latest meta-analysis was the only one who performed a separate effect-modification analysis using data from four randomized trials.[6] There was no evidence for genotype-treatment interaction in clopidogrel users for the composite cardiovascular outcome. These results are in line with our conclusion and further substantiate there is no evidence that *CYP2C19* loss-of-function alleles are associated with worse outcomes in clopidogrel users.

Evaluating Discordant Meta-Analyses

The popularity of meta-analyses in the cardiovascular field has increased by almost 1800% over the past 20 years, whereas the number of randomized controlled trials (RCTs) only increased by 140% over the same time period.[12] This practice leads to increasing duplication of meta-analyses on the same topic.[53] A recent study showed that 67% of the reviewed meta-analyses had at least one overlapping and 5% of the topics were studied in at least eight overlapping meta-analyses.[11] While overlapping meta-analyses may seem unnecessary, our review shows that authors make different choices in their conduct. Since there is no single best way how to define inclusion and exclusion criteria, how to define and select study populations and endpoints, and how to interpret heterogeneity and bias in light of the results, the variety in meta-analyses might be as wide-ranging as that in primary studies. When the variety in meta-analyses results from informed choices about the definitions, selection criteria, and analyses, this variety reflects paradigms in the field and should not be seen as duplication. Greater awareness and understanding of the subjectivity of meta-analyses and the impact of methodological choices on their results will enhance the appreciation of meta-analyses as high level of evidence.[12]

In 2010, the US Food and Drug Administration recommended *CYP2C19* genotyping for individualized antiplatelet management.[4, 6] Based on a re-evaluation of then-current and later meta-analyses we conclude that this recommendation is currently not evidence-

based. The GRAVITAS, ARCTIC and TRILOGY-ACS trials have shown that bedside platelet reactivity testing did not result in clinical benefits,[54-56] but recently a trial randomized patients undergoing PCI to either point-of-care genotyping and subsequent personalized treatment or standard clopidogrel treatment.[57] The point-of-care genotyping strategy showed significantly lower on-treatment platelet reactivity in *CYP2C19* loss-of-function carriers than the standard treatment strategy. However, the genetic substudy of the ARCTIC trial showed no benefits of genotyping.[58] In the absence of evidence that *CYP2C19* loss-of-function alleles truly affect outcomes, it will be interesting to see whether larger future trials of personalized treatment based on platelet monitoring and genotyping can show improvement in clinical endpoints.

Conclusion

The current study systematically evaluated overlapping discordant meta-analyses on the same topic. The results and conclusions of 11 overlapping meta-analyses on the association between *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel are discordant. Effect sizes differed because some meta-analyses did not include data from conference abstracts and more recent meta-analyses included more primary studies. Yet, conclusions predominantly differed because between-study heterogeneity and bias were handled differently across meta-analyses. Confidence in the presence of an association is limited and personalized antiplatelet management based on genotyping is not supported by the currently available evidence.

ACKNOWLEDGEMENTS

We thank Pieter Wisse, Kim Wervers, and Jessie Huizer for their assistance in searching the literature.

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APPENDIX

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Supplementary Table 1. Mapping of Overlap across the Eleven Meta-Analyses Studying the Association between CYP2C19 and Clinical Outcomes

Primary studies				Meta-analyses, First author[ref], Search date										
Author	Publication date	Abstract[†]	Times included (%)	Hulot[1] Oct 2009	Jin[2] Dec 2009	Sofi[3] Jan 2010	Mega[4] Aug 2010	Zabalza[5] Oct 2010	Bauer[6] Dec 2010	Liu[7] May 2011	Singh[8] May 2011	Jang[9] Sept 2011	Yamaguchi[10] Oct 2011	Holmes[11] Oct 2011
Mega[12]	March 2008	Yes	27	No	No (A)	No	Yes	No (A)	No (A)	Yes	No	Yes	No (A)	No
Trenk[13]	May 2008	No	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Malek[14]	Jul 2008	No	64	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Simon[15]	Dec 2008	No	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Collet[16]	Dec 2008	No	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Giusti[17]	Jan 2009	No	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mega[18]	Jan 2009	No	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Sibbing[19]	Feb 2009	No	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Anderson[20]	March 2009	Yes	45	Yes	No (A)	No	Yes	No (A)	No (A)	Yes	Yes	No	No (A)	Yes
Shuldiner[21]	Aug 2009	No	91	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Worrall[22]	Sept 2009	Yes	36	Yes	No (A)	No	No	No (A)	No (A)	Yes	Yes	No	No (A)	Yes
Bhatt[23]	Sept 2009	Yes	45	Yes	No (A)	No	No	No (A)	No (A)	Yes	Yes	No	No (A)	Yes
Paré CURE[24]	Aug 2010	No	55					Yes	Yes	Yes	Yes	Yes	No	Yes
Paré ACTIVE-A[24]	Aug 2010	No	18					No	No	Yes	No	No	No	Yes
Tiroch[25]	Sep 2010	No	45					Yes	Yes	Yes	No	No	Yes	Yes
Ko[26]	Sep 2010	Yes	9					No (A)	No (A)	No	No	Yes	No (A)	No
Wallentin[27]	Oct 2010	No	55					Yes	Yes	Yes	Yes	Yes	No	Yes
Malek[28]	Oct 2010	No	18						No	No	No	No	Yes	Yes
Sawada[29]	Nov 2010	No	36						Yes	Yes	No	Yes	No	Yes
Yamamoto[30]	Dec 2010	No	18						No	Yes	Yes	No	No	Yes (E)

Supplementary Table 1. Mapping of Overlap across the Eleven Meta-Analyses Studying the Association between CYP2C19 and Clinical Outcomes (*continued*)

Primary studies				Meta-analyses, First author[ref], Search date										
Author	**Publication date**	**Abstract†**	**Times included (%)**	**Hulot[1] Oct 2009**	**Jin[2] Dec 2009**	**Sofi[3] Jan 2010**	**Mega[4] Aug 2010**	**Zabalza[5] Oct 2010**	**Bauer[6] Dec 2010**	**Liu[7] May 2011**	**Singh[8] May 2011**	**Jang[9] Sept 2011**	**Yamaguchi[10] Oct 2011**	**Holmes[11] Oct 2011**
Bouman B[31]	Dec 2010	No	9						Yes	No	No	No	No	No
Komarov[32]	April 2011	Yes	9							No	No	No	No (A)	Yes
Nishio[33]	April 2011	Yes	9							No	No	Yes	No (A)	No
Campo[34]	June 2011	No	18									No	Yes	Yes
Oh[35]	June 2011	No	27									Yes	Yes	Yes
Tang[36] / Yuan[37]	July 2011/ Sep 2011	Yes	18									Yes	No (A)	Yes
Ono[38]	Aug 2011	No	9									No	No	Yes (E)
Harmsze[39]	Oct 2011	No	09										No	Yes
Jeong[40]	Nov 2011	No	9											Yes
Tello-Montoliu[41]	Nov 2011	No	9											Yes
N of included studies				**10**	**8**	**7**	**9**	**11**	**12**	**18**	**14**	**16**	**7**	**27**
Percentage of all available studies included (%)				**83**	**67**	**58**	**75**	**65**	**57**	**78**	**61**	**59**	**25**	**90**

The opaque block represents papers that could not be included because the publication date of the study was later than the search date of the meta-analysis.
Annotations: (A) The primary study was not included in the meta-analysis because abstracts were considered ineligible, either explicitly stated (Zabalza and Bauer) or implicitly by systematically excluding abstracts (Jin, and Yamaguchi). (E) The primary study was identified in the study selection, but not included in the meta-analyses, because the wildtype genotype group had no events. The meta-analysis effectively included 25 studies.

Supplementary Table 2. Mapping of Overlap across the Eleven Meta-Analyses studying the Association between *CYP2C19* and Stent Thrombosis

Primary studies				Meta-analyses, First author[ref], Search date										
Author	**Publication date**	**Article provides effect measure or n events**	**Times included (%)**	**Hulot[1] Oct 2009**	**Jin[2] Dec 2009**	**Sofi[3] Jan 2010**	**Mega[4] Aug 2010**	**Zabalza[5] Oct 2010**	**Bauer[6] Dec 2010**	**Liu[7] May 2011**	**Singh[8] May 2011**	**Jang[9] Sept 2011**	**Yamaguchi[10] Oct 2011**	**Holmes[11] Oct 2011**
Trenk[13]	May 2008	No	45	No	No	No	Yes	No	No	No	No	Yes	No	No
Malek[14]	Jul 2008	No	55	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Collet[16]	Dec 2008	Yes	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Mega[18]	Jan 2009	Yes	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Sibbing[19]	Feb 2009	Yes	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Giusti[17]	Jan 2009	Yes	100	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shuldiner[21]	Aug 2009	No	45	No	No	No	Yes	No	No	No	No	Yes	No	No
Sibbing[42]	Jan 2010	Yes	36				No	No	No	No	No	No	No	Yes
Harmsze[43]	Sep 2010	Yes	27					Yes	Yes	Yes	No	No	No	Yes
Tiroch[25]	Sep 2010	Yes	36					Yes	Yes	Yes	No	No	Yes	Yes
Wallentin[27]	Oct 2010	Yes	45					Yes	Yes	Yes	Yes	Yes	No	Yes
Sawada[29]	Nov 2010	No	18						No	Yes	No	Yes	No	Yes
Bouman A[31]	Dec 2010	Yes	18						Yes	No	No	No	No	Yes
Bouman B[31]	Dec 2010	Yes	18						Yes	No	No	No	No	No
Sibbing[44]	April 2011	Yes	9							No	No	No	No	Yes
Campo[34]	June 2011	Yes	18									No	Yes	Yes
Oh[35]	June 2011	Yes	27									Yes	Yes	Yes
N of included studies				**4**	**5**	**4**	**6**	**7**	**9**	**9**	**6**	**10**	**5**	**14**
Percentage of all available studies included (%)				**57**	**71**	**57**	**75**	**64**	**64**	**60**	**40**	**59**	**29**	**82**

The opaque block represents papers that could not be included because the publication date of the study was later than the search date of the meta-analysis.

Supplementary Table 3. Characteristics of Primary Studies on *CYP2C19* and Clinical Outcomes

First author[ref]	Publication date	Design	Follow-up (m)	Patient Characteristics								Definition clinical outcomes							N of events (%)
				Patients, n	Age, mean (SD), yr	PCI, %;	Sex, % men	Smoking, % yes	Hypertension, % yes	Dyslipidemia, % yes	Diabetes, % yes	CV-Death	All-cause Death	MI	Revascularization	Stroke (ischemic)	ST	Other[a]	
Mega[12]	March 2008	RCT	1	227	60 (11)	58	78	44	NR	NR	17	✓		✓		✓			18 (8)
Trenk[13]	May 2008	Cohort	12	797	66 (10)	100	78	11	82	NR	25		✓	✓					24 (3)
Malek[14]	Jul 2008	Cohort	12	105	60 (NR)	100	71	45	51	34	17	✓		✓					6 (6)
Simon[15]	Dec 2008	Cohort	12	2208	66 (14)	70	71	55	58	49	32		✓	✓		✓			294 (13)
Collet[16]	Dec 2008	Cohort	35	259	40 (5)	73	92	56	20	54	10	✓		✓	✓				26 (10)
Giusti[17]	Jan 2009	Cohort	6	772	68 (11)	100	75	34	65	60	22	✓							18 (2)
Mega[18]	Jan 2009	RCT	15	1459	60 (11)	95	71	38	66	49	22	✓		✓		✓			129 (9)
Sibbing[19]	Feb 2009	RCT	1	2485	67 (10)	100	78	16	63	49	36		✓	✓					173 (7)
Anderson[20]	March 2009	Cohort	12	1250	63 (12)	100	73	18	NR	NR	28	✓		✓		✓			209 (17)
Shuldiner[21]	Aug 2009	Cohort	12	228	64 (12)	100	60	25	NR	NR	38	✓		✓		✓			10 (4)
Worrall[22]	Sept 2009	Cohort	12	104	NR	100	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10 (10)
Bhatt[23, 45]	Sept 2009	RCT	28	2428	64 (NR)	28	70	21	28	NR	43	✓		✓		✓			153 (6)
Paré CURE[24]	Aug 2010	RCT	NR	5059	64 (11)	15	59	22	NR	NR	21	✓		✓		✓			541 (11)
Paré ACTIVE-A[24]	Aug 2010	RCT	43	1156	71 (10)	0	55	8	NR	NR	21	✓		✓		✓		✓	275 (24)
Tiroch[25]	Sep 2010	Cohort	12	928	65 (NR)	98	75	37	75	52	24		✓	✓				✓	82 (9)
Ko[26]	Sep 2010	NR	12	2176	NR	NR	NR	NR	NR	NR	NR		✓	✓		✓			84 (4)
Malek[28]	Oct 2010	RCT	12	4904	63 (11)	61;	69	36	65	47	23	✓		✓		✓			481 (10)
Wallentin[27]	Oct 2010	Cohort	48	261	60 (11)	100	67	35	74	64	28		✓						30 (12)

Supplementary Table 3. Characteristics of Primary Studies on *CYP2C19* and Clinical Outcomes (*continued*)

				Patient Characteristics								Definition clinical outcomes							
First author[ref]	Publication date	Design	Follow-up (m)	Patients, n	Age, mean (SD), yr	PCI, %;	Sex, % men	Smoking, % yes	Hypertension, % yes	Dyslipidemia, % yes	Diabetes, % yes	CV-Death	All-cause Death	MI	Revascularization	Stroke (ischemic)	ST	Other[a]	N of events (%)
Sawada[29]	Nov 2010	Cohort	8	100	70 (NR)	100	85	41	81	69	42		✓	✓	✓				26 (26)
Yamamoto[30]	Dec 2010	Cohort	12	123	69 (10)	80	66	16	78	61	49	✓		✓		✓			5 (5)
Bouman B[31]	Dec 2010	Cohort	12	1982	62 (10)	100	71	36	63	55	24	✓		✓		✓			216 (11)
Komarov[32]	April 2011	Cohort	18	399	59 (NR)	NR;	NR	NR	NR	NR	NR	✓			✓	✓			70 (18)
Nishio[33, 46]	April 2011	Cohort	NR	125	70 (***)	100	76	39	83	68	47				✓		✓		9 (7)
Campo[34]	June 2011	Cohort	12	300	66 (13)	100	77	24	72	51	24		✓	✓		✓			31 (7)
Oh[35]	June 2011	Cohort	12	2146	61 (10)	100	66	25	60	46	30	✓		✓	✓				208 (10)
Tang[36] **/ Yuan**[37]	July 2011/ Sep 2011	Cohort	12	267	[b]	100	[b]	[b]	[b]	[b]	[b]		✓	✓	✓		✓	✓	14 (5)
Ono[38]	Aug 2011	Cohort	12	202	69 (10)	100	75	22	81	76	40	✓		✓		✓		✓	2 (1)
Harmsze[39]	Oct 2011	Cohort	12	725	63(10)	65	76	10	75	81	17		✓	✓		✓	✓		NR
Jeong,[40]	Nov 2011	Cohort	21	266	63 (12)	91	73	53	47	27	26	✓		✓		✓			13 (5)
Tello-Montoliu[41]	Nov 2011	Cohort	6	428	67 (12)	46	90	19	76	60	46	✓						✓	97 (24)

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; DES, drug-eluting stent; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; ST, stent thrombosis; UAP, unstable angina pectoris.

a). The other clinical outcomes included unstable angina pectoris (n=1), recurrent acute coronary syndrome (n=2) or systemic embolism (n=2).

b). abstract in English, article in Chinese. Tang is the abstract that preceded the publication by Yuan. The data in the table is based on the English conference abstract and the English abstract of the article.

Supplementary Table 4. Main Results and Conclusions for Clinical Endpoints and Stent Thrombosis

First author[ref]	Publication date	Model	Main result (95% CI)	Conclusion about the presence of association	
				Yes/no	Description (Abstract/Discussion)
Clinical endpoint					
Hulot[1]	July 2010	Random Fixed	1.45 (1.12-1.89) 1.29 (1.12-1.49)	Possible	"[...] reduced *CYP2C19* function appears to expose clopidogrel treated patients to excess cardiovascular risk and mortality. Conflicting results among studies may be explained by differences in types and/or levels of risk of patients." (Abstract)
Jin[2]	Sept 2010	Random	1.46 (1.01-2.13)	Yes	"*CYP2C19*2* carrier status is significantly associated with an increased risk of adverse cardiovascular events." (Abstract)
Mega[4]	Oct 2010	Random	1.57 (1.13-2.16)	Possible	"Carriage of even one reduced-function *CYP2C19* allele appears to be associated with a significantly increased risk of MACE." (Abstract)
Sofi[3]	June 2011	Random Fixed	1.96 (1.14-3.37) 1.33 (1.09-1.61)	Yes	"[...] the *CYP2C19*2* polymorphism is associated with an increased risk of MACE and ST." (Abstract)
Zabalza[5]	June 2011	Random	1.23 (0.97-1.55)	No	"The results question the relevance of the *CYP2C19* LOF alleles in the prediction of major cardiovascular events [...]." (Abstract)
Liu[7]	July 2011	Random	1.26 (1.06-1.50)	Yes	"[...] our analysis included more studies and more widely supported the conclusion that CYP2C19 loss-of-function alleles increase the rate of MACE and stent thrombosis." (Letter)
Bauer[6]	Aug 2011	Random Fixed	1.11 (0.89-1.39) 1.07 (0.96-1.19)	No	"[...] does not indicate a substantial or consistent influence of *CYP2C19* gene polymorphisms on the clinical efficacy of clopidogrel." (Abstract)
Holmes[11]	Dec 2011	Random Fixed	1.34 (1.15-1.56) 1.18 (1.09-1.28)	No	"[...] overall there was no significant association of [the] genotype with cardiovascular events." (Abstract)
Jang[9]	May 2012	Random	1.42 (1.13-1.78)	Yes	"[...] carrier status for LOF *CYP2C19* is associated with an increased risk of adverse clinical events in patients [...]." (Abstract)
Singh[8]	June 2012	Random	1.28 (1.07-1.55)	Yes	"[...] *CYP2C19*2* polymorphism is associated with significantly increased adverse CV events." (Abstract)
Yamaguchi[10]	July 2012	None	Not performed	No	"An association between the CYP2C19 polymorphism and clinical outcome was not observed [...]." (Discussion)

Supplementary Table 4. Main Results and Conclusions for Clinical Endpoints and Stent Thrombosis (*continued*)

First author[ref]	Publication date	Model	Main result (95% CI)	Conclusion about the presence of association	
				Yes/no	Description (Abstract/Discussion)
Stent thrombosis					
Hulot[1]	July 2010	Random Fixed	3.45 (2.13-5.57) 3.45 (2.14-5.57)	Yes	"The hazard of reduced-function *CYP2C19* allele carriage was even more striking for ST [...]." (Discussion)
Jin[2]	Sept 2010	Fixed	3.81 (2.27-6.40)	Yes	"[...] We also noted a marked higher rate of ST in patients carrying at least one *CYP2C19*2* allele." (Discussion)
Mega[4]	Oct 2010	Random	2.81 (1.81-4.37)	Yes	"Carriage of even one reduced-function *CYP2C19* allele appears to be associated with a significantly increased risk of MACE, particularly ST." (Abstract)
Sofi[3]	June 2011	Fixed	3.82 (2.23-6.54)	Yes	"[...] the *CYP2C19*2* polymorphism is associated with an increased risk of MACE and ST." (Abstract)
Zabalza[5]	June 2011	Random	2.24 (1.52-3.30)	Yes	"The results question the relevance of the *CYP2C19* LOF alleles in the prediction of major cardiovascular events beyond ST [...]." (Abstract)
Liu[7]	July 2011	Random	2.58 (1.77-3.77)	Yes	" [...] our analysis included more studies and more widely supported the conclusion that *CYP2C19* loss-of-function alleles increase the rate of MACE and stent thrombosis." (Letter)
Bauer[6]	Aug 2011	Random Fixed	1.77 (1.31-2.40) 1.67 (1.34-2.08)	No	"Specifically, the association of ST with LOF genotypes was subject to bias from small study effects and to interaction with publication year. Adjustment for these quality modifiers tended to abolish the association." (Discussion)
Holmes[11]	Dec 2011	Random Fixed	1.88 (1.46-2.41) 1.75 (1.50-2.03)	Possible	"This [...] meta-analysis does not demonstrate a clinically important association [...] with the possible exception of ST." (Discussion)
Jang[9]	May 2012	Fixed	2.41 (1.76-3.30)	Yes	"[...] carriers of ≥1 *CYP2C19* LOF allele have two times greater mortality and ST compared to wild-type homozygote carriers." (Discussion)
Singh[8]	June 2012	Fixed	2.41 (1.70-3.41)	Yes	"Our meta-analyses indicates that *CYP2C19**2 polymorphism results in significantly increased risk of cardiovascular events like MI, ST and CV deaths."(Discussion)
Yamaguchi[10]	July 2012	Fixed	2.65 (1.46-4.84)	Yes	"[...] *CYP2C19*2* carrier status was associated with ST only." (Discussion)

Abbreviations: CI, confidence interval; ST, stent thrombosis; LOF, loss-of-function; MACE, major adverse cardiovascular event;
Model indicates whether effect estimates were obtained using random or fixed effect models. Main results are odds ratios or hazard ratio according to each of the meta-analyses.

References for Appendix

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CHAPTER 21

Review and Recommendations on the Current Practice of Meta-Analyses: a guide to appraise the evidence

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EuroIntervention. 2014;9:1013-20.

ABSTRACT

Meta-analyses aim to summarize the totality of findings on a specific research question and are considered the highest level of evidence. Over the past two decades, all medical disciplines, including the cardiovascular field, have witnessed an explosive dissemination of meta-analyses that outpaced increasing number of other study types such as randomized controlled trials. This trend entailed the publication of duplicate meta-analyses on the same topic. Although some replication of research is generally warranted, a large number of overlapping (discordant) meta-analyses reflects waste of resources, adds confusion to the field and threatens the value of the study design. In this review, we stress that considerations regarding heterogeneity, publication bias and quality of primary studies serve as a basis to appraise the evidence across overlapping meta-analyses. A flowchart is presented to help interpret the evidence. To maintain the appreciation of meta-analyses as the highest level of evidence, authors should adhere to the appropriate reporting guideline, describe the rationale for performing the (updated) meta-analysis, register their project in a dedicated database and evaluate the whole body of evidence.

INTRODUCTION

Systematic reviews and meta-analyses identify, appraise and synthesize all evidence on a specific research question. They are considered the highest level of evidence, help physicians stay up to date and enable them to make informed clinical decisions.[1] It is therefore not surprising that this study design has become increasingly popular.[2, 3]

Inevitably the phenomenon of duplicate meta-analyses is also increasingly common. A recent study showed that more than half of meta-analyses have at least one overlapping meta-analysis, and some topics had up to 13 overlapping meta-analyses.[2] While some degree of duplication is warranted in research, large numbers of overlapping meta-analyses seem unnecessary and could reflect wasted efforts and inefficiency in the process of summarizing evidence.[2] In addition, the interpretation of evidence becomes confusing if the conclusions of duplicate meta-analyses are discordant.

In this paper, we review the current practice of meta-analyses in cardiovascular medicine, the implications of overlapping meta-analyses, and provide recommendations on the interpretation and prioritization of (duplicate) meta-analyses.

THE INCREASING POPULARITY OF META-ANALYSES

The increasing popularity of meta-analyses is illustrated in Figure 1. A PubMed search showed that the number of meta-analyses in the cardiovascular field has increased almost 1800% between 1993 and 2012, whereas the number of randomized controlled trials (RCTs) increased by only 140% in the same time period. In 1993, on average 28 RCTs were published for every meta-analysis, whereas this RCT:meta-analysis ratio was 2.7:1 in 2012. This trend is an indication of the relative growth of meta-analyses as compared with other published research and was seen in both the cardiovascular discipline (Figure 1B), as well as in other medical disciplines (Figure 1A). Between 1993 and 2013, on average 18% of all meta-analyses concerned a cardiovascular topic. This proportion remained stable over time.

The increasing popularity led to duplicate meta-analyses on the same topic.[4] A recent study investigated overlapping meta-analyses on the same topic by assessing a randomly selected 5% of all published meta-analyses in 2010. The authors found that 67% of all meta-analyses had at least one overlapping meta-analysis that did not represent an update and 5% of the research questions were investigated in at least eight overlapping meta-analyses.[2] Replication of research generally leads to more knowledge and confidence in the

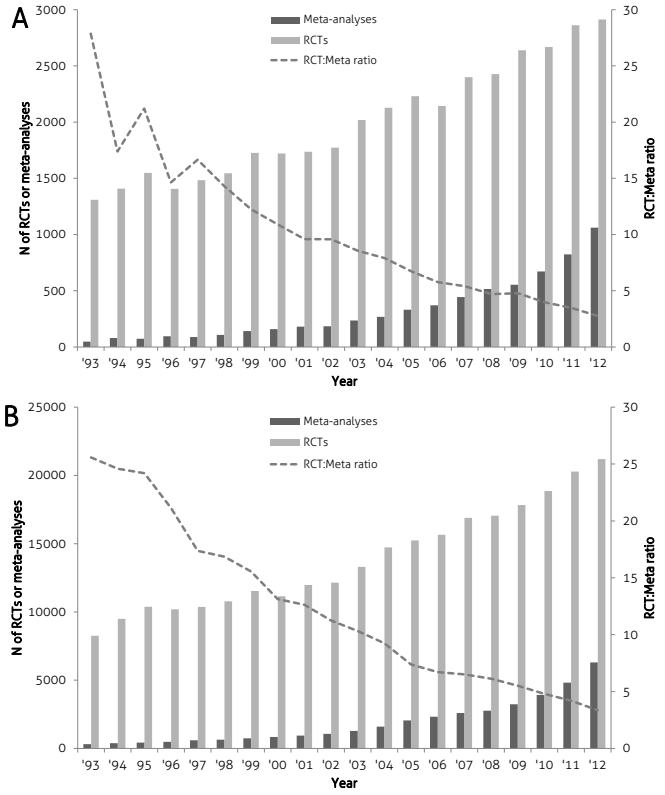

Figure 1. Number of Annually Published Meta-Analyses and RCTs in (A) the Cardiovascular Field and (B) all Disciplines

The red and blue bars represent the annually published RCTs and meta-analyses, respectively. The green line represents the number of published meta-analyses compared with the number of published RCTs in each year. It is an indication of the relative growth of meta-analyses as compared with the overall growth of published research in the cardiovascular field. Data is based on the following PubMed searches: A: (randomi* OR meta-analysis [ptyp]). B: (randomi* OR meta-analysis [ptyp]) ("Cardiovascular Diseases"[Mesh]). N, number; RCT, randomized controlled trial.

conclusions, but could also represent wasted time and effort. Some authors suggest that four or more meta-analyses on the same topic with similar eligibility criteria and outcomes is too many, but there is no specific number regarding the correct amount of duplication.[4]

EXAMPLES OF OVERLAPPING META-ANALYSES

Two case-examples of overlapping meta-analyses in the cardiovascular field are illustrated in Table 1 (Supplementary Table 1) and Table 2 (Supplementary Table 2), respectively. For each meta-analysis, we extracted information on the year of publication, search date,

Table 1. Overlapping Meta-Analyses on Intracoronary versus Intravenous Administration of Abciximab

	Hansen et al[5]	Navarese et al[7]	Shimada et al[8]	De Luca et al[6]	De Rosa et al[9]	Kubica et al[10]	Wang et al[11]	Piccolo et al[12]
Publication date	2010	2012	2012	2012	2012	2012	2013	2013
Search date	November 2009	March 2011	August 2011	December 2011	March 2012	April 2012	May 2012	NA
Effect (95% CI) for MACE	0.62 (0.38-1.03)	NA	0.59 (0.27-1.28)	NA	0.47 (0.31-0.71)	NA	0.55 (0.40-0.76)	NA
Effect (95% CI) for mortality	0.57 (0.35-0.94)	0.43 (0.20-0.94)	0.44 (0.20-0.95)	0.85 (0.59-1.23)	0.42 (0.20-0.86)	0.67 (0.34–1.34)	0.69 (0.45-1.07)	0.77 (0.51-1.17)
Effect (95% CI) for myocardial infarction	NA	0.54 (0.23-1.28)	NA	0.79 (0.46-1.33)	NA	0.61 (0.40-0.92)	0.59 (0.37-0.93)	NA
Effect (95% CI) for repeat revascularization	NA	0.53 (0.29-0.99)	NA	NA	NA	0.66 (0.40-1.09)	0.64 (0.32-1.29)	NA
Effect (95% CI) for major bleeding	NA	0.91 (0.46-1.79)	NA	1.19 (0.76-1.87)	NA	1.18 (0.76-1.83)	1.00 (0.57-1.74)	NA
Screened studies	979	2,351	37	1,865	48	6,562	660	NA
Pooled patients	2,301	1,246	1,148	3,259	4,226	3,331	3,916	3,158
Studies included	5 RCTs, 3 OSs	6 RCTs	4 RCTs	8 RCTs	10 RCTs	7 RCTs	9 RCTs	5 RCTs
Statistical approach	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist
Type	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study- and Patient-level

For the selection of overlapping meta-analyses of intracoronary vs. intravenous administration of Abciximab in patients with acute coronary syndromes we searched PubMed for meta-analyses of randomized controlled trials and/or observational studies published any time using the search terms Abciximab [Title] AND meta-analysis [Title/abstract] AND intracoronary [Title/abstract] without language restrictions. Effect estimates are reported for intracoronary vs. intravenous administration. An extension of this table, including the primary studies in each meta-analyses is available in the appendix (Supplementary Table 1).

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; NA, not available; OSs observational studies; PCI, percutaneous coronary intervention; RCTs, randomized controlled trials; STEMI, ST-segment elevation myocardial infarction.

Table 2. Overlapping Meta-Analyses on PCI versus CABG in Patients with Left Main Coronary Artery Disease

	Biondi-Zoccai et al[13]	Naik et al[14]	Lee et al[18]	Capodanno et al[15]	Ferrante et al[16]	Kajimoto et al[17]	Jang et al[21]	Gao et al[20]	Alam et al[19]	Desch et al[22]	Sa et al[23]	Bittl et al[24]
Publication date	2008	2009	2010	2011	2011	2012	2012	2012	2013	2013	2013	2013
Search date	September 2006	December 2008	June 2009	April 2011	NA	May 2011	July 2011	October 2011	January 2011	April 2011	2011	NA
Effect (95% CI) for MACCE	0.46 (0.24-0.90)	1.16 (0.68–1.96)	NA	1.28 (0.95-1.72)	1.24 (0.93-1.67)	0.55 (0.43-0.70)*	NA	NA	1.20 (0.92-1.56)	1.26 (1.02-1.57)	1.61 (NA), p<0.001	NA
Effect (95% CI) for mortality	NA	1.11 (0.66–1.85)	1.12 (0.80-1.56)*	0.74 (0.43-1.29)	0.72 (0.42-1.24)	0.92 (0.60-1.40)*	0.68 (0.45-1.02)	0.97 (0.81-1.15)	0.81 (0.62-1.06)	0.74 (0.46-1.19)	0.69 (NA), p=0.05	1.01 (0.68-1.45)
Effect (95% CI) for MI	NA	NA	0.70 (0.45-1.09)*	0.98 (0.54-1.78)	0.97 (0.54-1.74)	0.67 (0.43-1.05)*	1.07 (0.65-1.76)	NA	1.32 (0.91-1.91)	1.19 (0.69-2.06)	NA	NA
Effect (95% CI) for Stroke	NA	NA	NA	0.15 (0.03-0.67)	0.14 (0.04-0.55)	NA	0.23 (0.09-0.58)	0.29 (0.16-0.51)	0.31 (0.20-0.49)	0.26 (0.10-0.69)	NA	NA
Effect (95% CI) for Rep Revasc	NA	4.01 (2.01–7.98)	0.44 (0.32-0.59)*	2.25 (1.54-3.29)	2.17 (1.48-3.17)	0.40 (0.30-0.55)*	3.52 (2.72-4.56)	4.44 (3.42-5.78)	3.73 (2.71-5.14)	1.94 (1.43-2.61)	3.60 (NA), p<0.001	NA
Screened studies	823	7,294	NA	254	189	106	472	76	355	1,236	9,120	12
Pooled patients	670	3,773	2,905	1,611	1,611	2,601	5,079	6,992	11,148	1,611	5,674	4,574
Studies included	3 OSs	2 RCTs, 8 OSs	2 RCTs, 8 OSs	4 RCTs	4 RCTs	3 RCTs	3 RCTs, 9 OSs	11 RCTs, 2 OSs	4 RCTs, 23 OSs	4 RCTs	3 RCTs, 13 OSs	4 RCTs, 8 OSs
Statistical approach	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Bayesian
Type	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level

For the selection of overlapping meta-analyses of PCI vs. CABG in patients with left main disease we searched PubMed for meta-analyses of randomized controlled trials and/or observational studies published any time using the search terms left main [Title] AND meta-analysis [Title/abstract] AND PCI [Title/abstract] without language restrictions. An extension of this table, including the primary studies in each meta-analyses is available in the appendix (Supplementary Table 2).

* Treatment effects are reported as PCI vs. CABG, except in the meta-analyses by Lee et al. and Kajimoto et al., in which treatment effects were reported as CABG vs. PCI.

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NA, not available; OSs observational studies; *p*=*p*-value; PCI, percutaneous coronary intervention; RCTs, randomized controlled trials; STEMI, ST-segment elevation myocardial infarction.

treatment effect for outcomes of interest, number of studies screened and selected, and patient population. We also noted first author, journal and year of publication of the studies included and combined in each meta-analysis.

Through a PubMed search, seven overlapping meta-analyses of intracoronary versus intravenous administration of abciximab in patients with acute coronary syndromes were identified.[5-11] An additional meta-analysis with patient-level data on the same topic is published in this issue of the Journal.[12] The meta-analyses were published between 2010 and 2013 (88% in 2012-2013), and the number of primary studies included ranged between four and ten (Table 2). Seven meta-analyses included only RCTs, and one meta-analysis comprised both RCTs and observational studies (OSs). The search dates ranged from November 2009 to May 2012, which was reflected in the number of screened studies (from 37 to 6,562). The treatment effect for mortality was reported in all meta-analyses but was of inconsistent statistical significance; four (50%) meta-analyses found a statistically significant benefit of intracoronary abciximab administration, whereas four studies (50%) did not. Similarly, the risk of major adverse cardiac events (MACE) was significantly reduced in only two of four (50%) meta-analyses reporting on this outcome, the risk of myocardial infarction in two of four (50%) and the risk of repeat revascularization in one of three (33%). Of four meta-analyses that sought to assess the risk of bleeding, none (0%) found a significant difference between intracoronary and intravenous administration.

Another PubMed search identified twelve meta-analyses of PCI vs. CABG in patients with left main coronary artery disease. These meta-analyses were published between 2008 and 2013 (58% in 2012-2013) and the number of primary studies included ranged between 3 and 27 (Table 3).[13-24] Four meta-analyses included only RCTs, one meta-analysis comprised only OSs and seven meta-analyses included both RCTs and OSs. The authors' search date varied from September 2006 to April 2011, and the number of screened studies ranged between 12 and 9,120. Mortality was reported in eleven meta-analyses, which all found no statistically significant benefits of either treatment. MACCE was reported in eight meta-analyses, of which three (38%), one (13%) and four (50%) found a higher, lower or similar risk for this composite endpoint after PCI versus CABG. All meta-analyses that reported an effect size for myocardial infarction (n = 7) found no statistically significant difference between treatments. Also, all ten meta-analyses that investigated repeat revascularization (N = 10) found significantly higher rates after PCI than after CABG. On the other hand, stroke was significantly higher with CABG in all six meta-analyses reporting this outcome.

Taken together, these findings indicate that meta-analyses on the optimal administration route for abciximab and the optimal treatment strategy for left main revascularization

published in the last 5 years differed not only in the magnitude of the treatment effect for some outcomes, but also occasionally in the direction of the effect (e.g. MACCE in the left main meta-analyses). In the illustrative examples above, these differences might be attributed to varying eligibility criteria regarding inclusion of OSs, the target population analyzed (e.g. acute coronary syndromes or ST-segment elevation myocardial infarction in the abciximab route meta-analyses; patients with diabetes mellitus or acute coronary syndromes in the left main revascularization meta-analyses) and the non-consideration of studies published after the search date of each meta-analysis. In contrast, while more recent meta-analyses might have included newly published studies, their incremental value remains uncertain (e.g., similar results were noted in all meta-analyses of left main revascularization with regards to all the components of MACCE). Interestingly, three meta-analyses of left main revascularization included exactly the same 4 RCTs but derived slightly different summary effects, underscoring the potential for differences introduced at the stage of data synthesis[15, 16, 22].

WHAT TO DO WHEN META-ANALYSES OVERLAP

Overlapping meta-analyses can result in uncertainty when they come to discordant conclusions. Discordance can occur at the level of results or interpretation, and the underlying sources are summarized in Table 3.[25, 26] Effect sizes can differ because some meta-analyses use slightly different eligibility criteria for study selection, such as the eligibility of abstracts or language restrictions. Perhaps more subtle are discordances due to handling and interpretation of heterogeneity and publication bias.

Table 3. Potential Sources of Discordance in Overlapping Meta-Analyses

Design	Analysis	Interpretation
Search (date, key words)	Summary measure (crude OR, HR, RR)	Interpretation of all results, including heterogeneity, publication bias and quality assessment
Information sources used (databases, abstracts from meetings)	Fixed/random effects analysis	Combining all results and linking this to the overall conclusion of the meta-analysis
Eligibility criteria	Heterogeneity assessment	
Data extraction (solitary/duplicate, retrieving unpublished data)	Publication bias assessment	
Study- or patient-level data	Quality assessment of primary studies	
Definitions, length of follow-up	Extensiveness of extra analyses (sensitivity analyses, meta-regression)	

OR, odds ratio; HR, hazard ratio; RR, relative risk.

Heterogeneity is an apparent difference between the results of the primary studies,[27, 28] and may be present when study populations, interventions, outcomes, or methodologies differ across the studies. Heterogeneity is generally quantified by the I^2 or Cochran's Q-statistic.[29] To evaluate heterogeneity, authors should not only examine the statistic, but also scrutinize potential sources of heterogeneity by comparing primary study characteristics, design, follow-up duration, patient characteristics and outcome definitions.[30] Meta-regression is a typical approach to relate sources of variation in heterogeneous treatment effects to specific study characteristics. However, study-level meta-analyses have some limitations in explaining heterogeneity, and using individual patient data in patient-level meta-analyses may lead to a more unbiased assessment.[31] In addition, patient-level meta-analyses allow better alignment of definitions and follow-up. This is illustrated by the above-mentioned meta-analysis by Piccolo et al., which pooled individual patient data from trials of intracoronary versus intravenous administration of abciximab, enabling investigation of detailed endpoints such as post-procedural Thrombolysis in Myocardial Infarction Study (TIMI) 3 flow, myocardial blush grade and complete ST-segment resolution.[12]

Publication bias is the tendency by investigators, reviewers and editors to submit or accept manuscripts for publication based on the direction or strength of the study findings.[32] Tests that assess publication bias include Funnel plots, Harbord-Egger tests, and trim and fill analyses.[33-35] If these tests identify missing studies with a smaller effect or an effect in the opposite direction, investigators should be very careful with their conclusions regarding the presence and/or direction of the association under study.

Discordant meta-analyses form challenges for authors, clinicians and editorial boards. Which meta-analysis is most applicable to the clinical question, and which one is methodologically most solid? A flowchart to help with the interpretation of discordant meta-analyses is provided in Figure 2.[26] When meta-analyses truly study the same question, the flowchart guides the reader to methodological appraisal of the discordant meta-analyses. Quality scoring lists might be useful as well, such as the Oxman Guyatt list and the AMSTAR checklist.[36, 37] These checklists can be used to map the methodological quality of meta-analyses. AMSTAR includes questions on design (e.g. "was there duplicate study selection and data extraction?";"was a comprehensive search performed?"), analysis (e.g. "was the scientific quality of the included studies documented?"; "were the methods used to combine the findings of the studies appropriate?"), and interpretation (e.g. "was the scientific quality of the included studies used appropriately in formulating conclusions?"). The use of scoring systems for assessing quality seems easy and attractive, and AMSTAR is a validated quality measurement tool. On the other hand, calculating these summary scores involve assigning weights to different items in the scale and thus

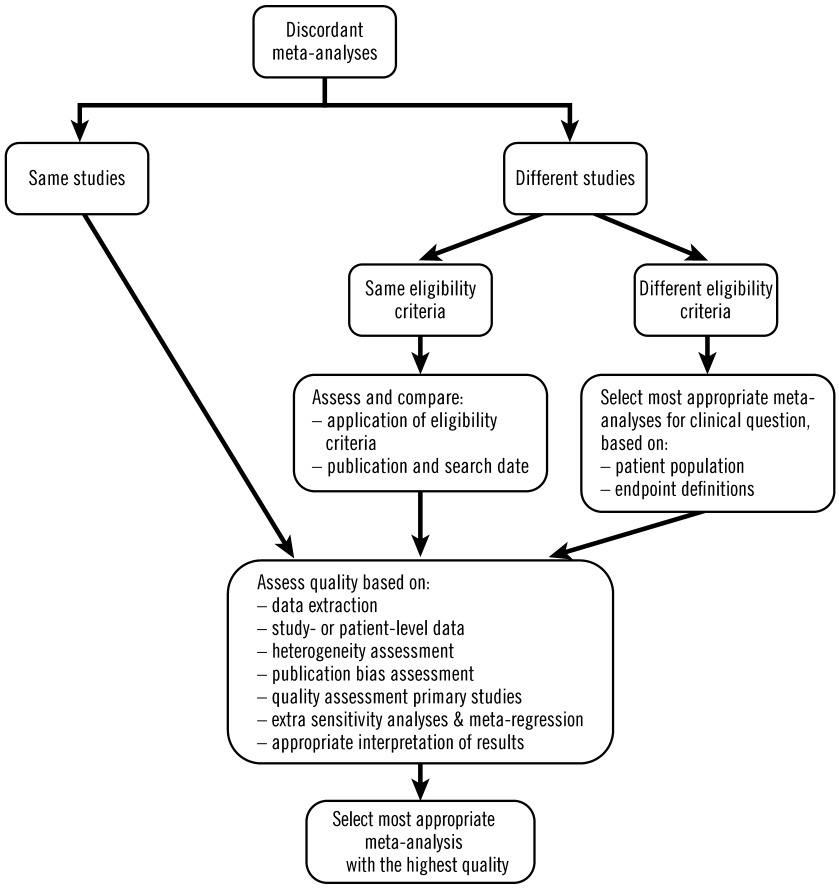

Figure 2. Flowchart for the Interpretation of Discordant, Overlapping Meta-Analyses
The flowchart helps the reader interpret overlapping, discordant meta-analyses, by guiding him/her to a methodological appraisal. Adapted from Jadad et al.[26]

prioritizing studies based on arbitrary assumptions. Using full reporting of how meta-analyses were rated based on each criterion is preferable.

HOW TO PRESERVE THE VALUE OF META-ANALYSES

A list of considerations for maintaining the value of meta-analyses and improve the quality of research in this field is provided in Table 4. Adherence to accepted guidelines for reporting is the essential to preserve the quality and value of meta-analyses. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, formerly QUOROM) statement consists of a 27-item checklist and a four-phase flow diagram aimed at improving the consistency and completeness of reporting of meta-analyses of RCTs.[38]

Table 4.

Maintaining the Value of Meta-Analyses
• Adhere to the PRISMA/MOOSE checklists
• Perform high quality analyses and interpret appropriately (see figure 2, table 3 and PRISMA/MOOSE)
• Reflect on timing when updating a meta-analysis
• Provide the rationale for performing a meta-analysis, referring to prior work
• Register the protocol in the PROSPERO registry
• Evaluate the whole body of evidence on a topic, not only small fragments

An analogous document has been elaborated by the MOOSE (Meta-Analysis Of Observational Studies In Epidemiology) group for meta-analyses of OSs.[39]

Because the evidence on a topic is typically dynamic and evolves over time, incorporation of new studies into an existing meta-analysis may lead to different conclusions.[40] Additional incentives for updating a meta-analysis may include the potential availability of new tools or markers to characterize subgroups,[41] the introduction of new outcome measures,[42] or even advances in the methodology for conducting a systematic review/meta-analysis.[24] However, the merits of publishing a new meta-analysis on the same topic needs to be evaluated, since redundant overlapping meta-analyses reflect waste of resources and potentially adds confusion. Authors of possibly overlapping meta-analyses should report the rationale for performing the meta-analysis (e.g. outdated and/or low quality previous meta-analyses). The PICO (Population, Intervention, Comparator, and Outcome) framework could be used to point out what aspect of the research question has changed. Optimal timing for a new meta-analysis depends on the speed of scientific progress in the specific field and the importance of the research question. Periodic literature surveillance, expert opinions and scanning of abstracts are helpful to identify new relevant evidences that may eventually be used for an updated meta-analysis. Once the need for updating a meta-analysis has been identified, the update should be performed properly and effectively. Technically, a previous search strategy can be useful and specific statistical methods for updating a meta-analysis have been described, such as "cumulative meta-analysis" and "null meta-analyses ripe for updating" approaches.[43, 44] Bayesian methodology for meta-analysis might provide a way to update and/or consolidate the evidence on a topic. In contrast to the frequentist approach, Bayesian statistics incorporates clinical judgment and pertinent information that would otherwise be excluded, and establishes inferences based on a wide range of flexible methods based on the theory of conditional probability.[24, 45, 46]

An important potential strategy to avoid multiplication of unnecessary meta-analyses is consultation of dedicated registries. For instance, the PROSPERO registry (http://www.crd.york.ac.uk/NIHR_PROSPERO) includes over 2,000 prospectively registered protocols of systematic reviews and meta-analyses in health and social care.[47-49] Registering meta-

analyses into a central database, similar to registration of trials into www.clinicaltrials.gov, helps to avoid unplanned duplication, increases transparency in the review process, and enables assessing the results of reported reviews versus what initially planned by the authors in the protocol. While authors increase the reputation of their work, journal editors are provided a safeguard against flawed methodologies.

Finally, meta-analyses should be comprehensive and not only evaluate small fragments of the evidence on a clinical question of interest.[50] To address this issue, umbrella reviews and network meta-analyses are gaining attention.[24, 51] Umbrella reviews consider multiple treatment comparisons for the management of the same disease or condition, with each comparison considered separately and clustered meta-analyses performed as appropriate.[52, 53] A treatment network typically uses nodes for each available treatment and each link between the nodes reflects a comparison of treatments in at least one or more primary studies. Compared with classic meta-analyses, umbrella reviews and network meta-analyses provide the reader with a wider vision on many treatments for a given condition, although typical limitations of standard meta-analyses (e.g. inherent bias of studies included, heterogeneity and publication bias) continue to apply.

CONCLUSIONS

The explosive dissemination of meta-analyses entailed the publication of duplicate meta-analyses on the same topic. The scope of a meta-analysis is to provide the reader with the most up-to-date evidence on the effect of an intervention and increase the statistical power of treatment comparisons for a given condition beyond that of individual studies, with the ultimate goal of informing clinical practice and guiding healthcare decisions. To reflect the evolving knowledge on a topic, meta-analyses are regularly updated as new studies become available. However, redundancy of overlapping meta-analyses on the same topic is frequently obvious and reflects waste of time, energies and economic resources. Considerations regarding heterogeneity, publication bias and quality of primary studies serve as a basis to appreciate the evidence across overlapping meta-analyses. Raising the quality of research is a collective effort of authors, peer-reviewers, editors and other players in the field. When preparing and submitting a meta-analysis, authors should take responsibility for advancing the field by adhering to the appropriate reporting guideline, report the rationale for performing the (updated) meta-analysis, register their project in a dedicated database and evaluate the whole body of evidence. Similarly, peer reviewers and editorial boards should carefully evaluate the additional merits of the meta-analysis under review over previous work, thereby filtering out inappropriate meta-analyses, avoiding confusion and maintaining the value of meta-analyses.

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APPENDIX

Table of Contents

Supplementary Table 1. Overlapping Meta-Analyses on Intracoronary versus Intravenous Administration of Abciximab

	Hansen et al[5]	Navarese et al[7]	Shimada et al[8]	De Luca et al[6]	De Rosa et al[9]	Kubica et al[10]	Wang et al[11]	Piccolo et al[12]
Publication date	2010	2012	2012	2012	2012	2012	2013	2013
Search date	November 2009	March 2011	August 2011	December 2011	March 2012	April 2012	May 2012	NA
Statistical approach	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist
Type	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study- and Patient-level
Effect size (95% CI) for MACE	0.62 (0.38-1.03)	NA	0.59 (0.27-1.28)	NA	0.47 (0.31-0.71)	NA	0.55 (0.40-0.76)	NA
Effect size (95% CI) for mortality	0.57 (0.35-0.94)	0.43 (0.20-0.94)	0.44 (0.20-0.95)	0.85 (0.59-1.23)	0.42 (0.20-0.86)	0.67 (0.34–1.34)	0.69 (0.45-1.07)	0.77 (0.51-1.17)
Effect size (95% CI) for myocardial infarction	NA	0.54 (0.23-1.28)	NA	0.79 (0.46-1.33)	NA	0.61 (0.40-0.92)	0.59 (0.37-0.93)	NA
Effect size (95% CI) for repeat revascularization	NA	0.53 (0.29-0.99)	NA	NA	NA	0.66 (0.40-1.09)	0.64 (0.32-1.29)	NA
Effect size (95% CI) for major bleeding	NA	0.91 (0.46-1.79)	NA	1.19 (0.76-1.87)	NA	1.18 (0.76-1.83)	1.00 (0.57-1.74)	NA
Screened studies	979	2,351	37	1,865	48	6,562	660	NA
Pooled patients	2,301	1,246	1,148	3,259	4,226	3,331	3,916	3,158
Studies included	5 RCTs, 3 OSs	6 RCTs	4 RCTs	8 RCTs	10 RCTs	7 RCTs	9 RCTs	5 RCTs
Wohrle et al, Circulation 2003	Yes	No	No	No	Yes	No	Yes	No
Kakkar et al, Catheter Cardiovasc Interv 2004	Yes	No	No	No	Yes	No	Yes	No
Bellandi et al, Catheter Cardiovasc Interv 2004	Yes	No	No	Yes	No	No	Yes	No
Galanche-Osuna et al, Rev Esp Cardiol 2006	Yes	No	No	No	Yes	No	Yes	No

Supplementary Table 1. Overlapping Meta-Analyses on Intracoronary versus Intravenous Administration of Abciximab (*continued*)

	Hansen et al[5]	Navarese et al[7]	Shimada et al[8]	De Luca et al[6]	De Rosa et al[9]	Kubica et al[10]	Wang et al[11]	Piccolo et al[12]
Studies included								
Thiele et al, Circulation 2008	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Bertrand et al, Int J Cardiol 2008	Yes	No	No	No	No	No	No	No
Dominguez-Rodriguez et al, Atherosclerosis 2009	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Iversen et al, (abstract) 2009	Yes	No	No	No	No	No	No	No
Gu et al, Circulation 2010	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bertrand et al, Am J Cardiol 2010	No	Yes	Yes	Yes	Yes	Yes	No	No
Dave et al, (abstract) 2010	No	Yes	No	Yes	No	Yes	No	No
Iversen et al, J Interv Cardiol 2011	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Iversen et al, Cardiology 2011*	No	No	No	No	Yes	Yes	Yes	No
Eitel et al, Clin Res Cardiol 2011*	No	No	No	No	Yes	Yes	No	No
Thiele et al, Lancet 2012	No	No	No	Yes	Yes	Yes	Yes	Yes

For the selection of overlapping meta-analyses of intracoronary vs. intravenous administration of Abciximab in patients with acute coronary syndromes we searched PubMed for meta-analyses of randomized controlled trials and/or observational studies published any time using the search terms Abciximab [Title] AND meta-analysis [Title/abstract] AND intracoronary [Title/abstract] without language restrictions. Effect estimates are reported for the longest follow-up available. Estimates effects are reported for intracoronary vs. intravenous administration.

* Represented long-term evaluation of previously published studies.

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; NA, not available; OSs observational studies; PCI, percutaneous coronary intervention; RCTs, randomized controlled trials; STEMI, ST-segment elevation myocardial infarction.

Supplementary Table 2. Overlapping Meta-Analyses on PCI versus CABG in Patients with Left Main Coronary Artery Disease

	Biondi-Zoccai et al[13]	Naik et al[14]	Lee et al[18]	Capodanno et al[15]	Ferrante et al[16]	Kajimoto et al[17]	Jang et al[21]	Gao et al[20]	Alam et al[19]	Desch et al[22]	Sa et al[23]	Bittl et al[24]
Publication date	2008	2009	2010	2011	2011	2012	2012	2012	2013	2013	2013	2013
Search date	September 2006	December 2008	June 2009	April 2011	NA	May 2011	July 2011	October 2011	January 2011	April 2011	2011	NA
Statistical approach	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Frequentist	Bayesian
Type	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level	Study-level
Effect size (95% CI) for MACCE	0.46 (0.24-0.90)	1.16 (0.68–1.96)	NA	1.28 (0.95-1.72)	1.24 (0.93-1.67)	0.55 (0.43-0.70)*	NA	NA	1.20 (0.92-1.56)	1.26 (1.02-1.57)	1.61 (NA), p<0.001	NA
Effect size (95% CI) for mortality	NA	1.11 (0.66–1.85)	1.12 (0.80-1.56)*	0.74 (0.43-1.29)	0.72 (0.42-1.24)	0.92 (0.60-1.40)*	0.68 (0.45-1.02)	0.97 (0.81-1.15)	0.81 (0.62-1.06)	0.74 (0.46-1.19)	0.69 (NA), p=0.05	1.01 (0.68-1.45)
Effect size (95% CI) for myocardial infarction	NA	NA	0.70 (0.45-1.09)*	0.98 (0.54-1.78)	0.97 (0.54-1.74)	0.67 (0.43-1.05)*	1.07 (0.65-1.76)	NA	1.32 (0.91-1.91)	1.19 (0.69-2.06)	NA	NA
Effect size (95% CI) for stroke	NA	NA	NA	0.15 (0.03-0.67)	0.14 (0.04-0.55)	NA	0.23 (0.09-0.58)	0.29 (0.16-0.51)	0.31 (0.20-0.49)	0.26 (0.10-0.69)	NA	NA
Effect size (95% CI) for repeat revascularization	NA	4.01 (2.01–7.98)	0.44 (0.32-0.59)*	2.25 (1.54-3.29)	2.17 (1.48-3.17)	0.40 (0.30-0.55)*	3.52 (2.72-4.56)	4.44 (3.42-5.78)	3.73 (2.71-5.14)	1.94 (1.43-2.61)	3.60 (NA), p<0.001	NA
Screened studies	823	7,294	NA	254	189	106	472	76	355	1,236	9,120	19
Pooled patients	670	3,773	2,905	1,611	1,611	2,601	5,079	6,992	11,148	1,611	5,674	4,574
Studies included	3 OSs	2 RCTs, 8 OSs	2 RCTs, 8 OSs	4 RCTs	4 RCTs	3 RCTs	3 RCTs, 9 OSs	11 RCTs, 2 OSs	4 RCTs, 23 OSs	4 RCTs	3 RCTs, 13 OSs	4 RCTs, 8 OSs

Supplementary Table 2. Overlapping Meta-Analyses on PCI versus CABG in Patients with Left Main Coronary Artery Disease (*continued*)

	Biondi-Zoccai et al[13]	Naik et al[14]	Lee et al[18]	Capodanno et al[15]	Ferrante et al[16]	Kajimoto et al[17]	Jang et al[21]	Gao et al[20]	Alam et al[19]	Desch et al[22]	Sa et al[23]	Bittl et al[24]
Studies included												
Gwon et al, J Kor Med Sci 2005	No	No	No	No	No	No	No	Yes	No	No	No	No
Lee et al, J Am Coll Cardiol 2006	Yes	No	Yes	No	No	No	Yes	No	No	No	Yes	No
Chieffo et al, Circulation 2006	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No	Yes
Palmerini et al, Am J Cardiol 2006	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No
Sanmartin et al, Am J Cardiol 2007	No	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes	Yes
Briguori et al, Am J Cardiol 2007	No	No	No	No	No	No	No	Yes	No	No	No	No
Lee et al, Int J Cardiol 2007	No	No	No	No	No	No	No	Yes	No	No	No	No
Palmerini et al, Eur Heart J 2007**	No	No	Yes	No	No	No	No	No	Yes	No	Yes	Yes
Seung et al, N Eng J Med 2008	No	Yes	Yes	No	No	No	Yes	No	No	No	Yes	Yes
Makikallio, Ann Med 2008	No	Yes	No	No	No	No	Yes	No	Yes	No	Yes	Yes

Supplementary Table 2. Overlapping Meta-Analyses on PCI versus CABG in Patients with Left Main Coronary Artery Disease (*continued*)

	Biondi-Zoccai et al[13]	Naik et al[14]	Lee et al[18]	Capodanno et al[15]	Ferrante et al[16]	Kajimoto et al[17]	Jang et al[21]	Gao et al[20]	Alam et al[19]	Desch et al[22]	Sa et al[23]	Bittl et al[24]
Studies included												
Daemen et al, J Am Coll Cardiol 2008**	No	No	No	No	No	No	No	Yes	No	No	No	No
Brener et al, Am J Cardiol 2008	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes
Hsu et al, Int Heart J 2008	No	No	No	No	No	No	No	No	Yes	No	No	No
White et al, JACC Interv 2008	No	Yes	No	No	No	No	No	No	Yes	No	Yes	Yes
Wu et al, Ann Thor Surg 2008	No	Yes	No	No	No	No	No	No	Yes	No	Yes	Yes
Buzman, J Am Coll Cardiol 2008	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes
Rodes-Cabau et al, Circulation 2008	No	No	No	No	No	No	No	No	Yes	No	No	No
Serruys et al (abstract) 2008	No	Yes	No	No	No	No	No	No	No	No	No	No
Boudriot et al, (abstract) 2008	No	No	Yes	No	No	No	No	No	No	No	No	No
Cheng et al, Circ J 2009	No	No	Yes	No	No	No	Yes	No	Yes	No	Yes	No

Supplementary Table 2. Overlapping Meta-Analyses on PCI versus CABG in Patients with Left Main Coronary Artery Disease (*continued*)

	Biondi-Zoccai et al[13]	Naik et al[14]	Lee et al[18]	Capodanno et al[15]	Ferrante et al[16]	Kajimoto et al[17]	Jang et al[21]	Gao et al[20]	Alam et al[19]	Desch et al[22]	Sa et al[23]	Bittl et al[24]
Studies included												
Buszman et al, J Am Coll Cardiol 2009	No	No	No	Yes	Yes	No	No	No	Yes	Yes	No	No
Serruys et al, N Engl J Med 2009	No	No	Yes	No	No	Yes	No	No	No	No	No	No
Dominguez-Franco et al, Rev Esp Cardiol 2009	No	No	No	No	No	No	No	Yes	No	No	No	No
Kin et al, JACC Interv 2009**	No	No	No	No	No	No	No	Yes	No	No	No	No
Qiao et al, (abstract) 2009	No	No	No	No	No	No	No	Yes	No	No	No	No
Tarantini et al, Cather Cardiovasc Int 2009	No	No	No	No	No	No	No	Yes	No	No	No	No
Ghenim et al, J Interv Cardiol 2009	No	No	No	No	No	No	No	No	Yes	No	Yes	No
Liu et al, Zhonghua Xin Xue Guan Bing Za Zhi 2009	No	No	No	No	No	No	No	No	Yes	No	No	No
Montalescot et al, Eur Heart J 2009	No	No	No	No	No	No	No	No	Yes	No	No	No

Supplementary Table 2. Overlapping Meta-Analyses on PCI versus CABG in Patients with Left Main Coronary Artery Disease (*continued*)

	Biondi-Zoccai et al[13]	Naik et al[14]	Lee et al[18]	Capodanno et al[15]	Ferrante et al[16]	Kajimoto et al[17]	Jang et al[21]	Gao et al[20]	Alam et al[19]	Desch et al[22]	Sa et al[23]	Bittl et al[24]
Studies included												
Wu et al, Am J Cardiol 2010	No	No	No	No	No	No	Yes	No	Yes	No	No	No
Kang et al, Am J Cardiol 2010	No	No	No	No	No	No	Yes	No	Yes	No	No	No
Morice et al, Circulation 2010**	No	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Park et al, N Engl J Med 2010	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Banning et al, J Am Coll Cardiol 2010**	No	No	No	No	No	No	No	Yes	No	No	No	No
Kapur et al, J Am Coll Cardiol 2010	No	No	No	No	No	No	No	Yes	No	No	No	No
Kapur et al, J Cardiovasc Med, 2010**	No	No	No	No	No	No	No	Yes	No	No	No	No
Yamagata et al, Circ J 2010	No	No	No	No	No	No	No	Yes	No	No	No	No
Chieffo et al, JACC Cardiovasc Interv 2010	No	No	No	No	No	No	No	No	Yes	No	Yes	No
Huang et al, Clin Res Cardiol 2010	No	No	No	No	No	No	No	No	Yes	No	No	No

Supplementary Table 2. Overlapping Meta-Analyses on PCI versus CABG in Patients with Left Main Coronary Artery Disease (*continued*)

	Biondi-Zoccai et al[13]	Naik et al[14]	Lee et al[18]	Capodanno et al[15]	Ferrante et al[16]	Kajimoto et al[17]	Jang et al[21]	Gao et al[20]	Alam et al[19]	Desch et al[22]	Sa et al[23]	Bittl et al[24]
Studies included												
Park et al, J Am Coll Cardiol 2010* **	No	No	No	No	No	No	No	No	Yes	No	No	No
Shimizu et al, Circ J 2010	No	No	No	No	No	No	No	No	Yes	No	Yes	No
Boudriot et al, J Am Coll Cardiol 2011	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Caggegi et al, Am J Cardiol 2011	No	No	No	No	No	No	Yes	No	Yes	No	Yes	No
Park et al, J Am Coll Cardiol 2011	No	No	No	No	No	No	No	Yes	Yes	No	No	No
Rittger et al, Clin Res Cardiol 2011	No	No	No	No	No	No	No	No	Yes	No	Yes	No
Pepe et al, Heart Vessels 2011	No	No	No	No	No	No	No	No	No	No	No	No

For the selection of overlapping meta-analyses of PCI vs. CABG in patients with left main disease we searched PubMed for meta-analyses of randomized controlled trials and/or observational studies published any time using the search terms left main [Title] AND meta-analysis [Title/abstract] AND PCI [Title/abstract] without language restrictions. Effect estimates are reported for the longest follow-up available.

* Treatment effects are reported as PCI vs. CABG, except in the meta-analyses by Lee et al. and Kajimoto et al., in which treatment effects were reported as CABG vs. PCI.
** subgroup analysis of previously published study. *** extended follow-up evaluation of previously published study.

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; NA, not available; OSs observational studies; *p*=*p*-value; PCI, percutaneous coronary intervention; RCTs, randomized controlled trials; STEMI, ST-segment elevation myocardial infarction.

CHAPTER 22

Methodologic Issues Regarding Background Mortality in Observational Studies

Osnabrugge RL, Head SJ, Kappetein AP.

J Thorac Cardiovasc Surg. 2011;142:1289-90.

TO THE EDITOR:

With great interest we read the article by Di Eusanio and associates[1] in a recent issue of the Journal. We congratulate the authors on their favourable results after aortic valve replacement (AVR) and the identification of predictors for post-operative mortality. However, some methodological issues exist concerning the comparison of survival rates with a reference population. The investigators use a static method to compare the three-year survival after AVR for octogenarians with the expected survival of an age- and gender-matched regional population and concluded that the survival was similar ($p = 0.157$).

Intuitively, survival after AVR is unlikely to be comparable to the general population. Patients undergoing heart valve replacement are vulnerable to valve and non-valve related events and the left ventricle of patients with aortic valve disease is characterized by progressive accumulation of interstitial myocardial fibrosis and impairment of myocyte ultrastructure leading to decreased survival. Aortic stenosis has been shown to be an inflammatory process associated with histopathological changes in the valve leaflets that are similar to those in other atherosclerotic diseases and the presence of calcific valve disease is associated with hypertension, diabetes, and the metabolic syndrome.[2] A survival comparable to the general population can therefore only be achieved by strict selection of patients undergoing AVR, which is the case in the study by Di Eusanio.

The major shortcoming in the static comparison method is that a dynamic cohort, the octogenarian study population, is compared with a static reference cohort from the regional life tables. Changes in the patient group caused by withdrawal at different times make the study cohort dynamic and need a rate-adjustment to make the comparison more accurate.[3-5] Rate-adjustment can be achieved by matching the reference cohort on age-, gender- and calendar time every moment an event occurs in the study population. When this mechanism is not taken into account then the benefit of treatment is overestimated. It would be interesting if the authors could compare the survival of the patient group with the age, gender- and calendar time-matched regional population using rate-adjustment.

Matching should not only be performed for age and gender, but also for other important demographic indicators such as race or socioeconomic class.[5] Unfortunately, this data is seldom available and consequently comparisons with the general population should be interpreted carefully.

Finally, we question some of the numbers and the corresponding figures in the article. Figure 1 shows a significant lower survival in Class III-IV as compared with class I-II ($p < 0.001$), whereas in the text a non-significant p-value of 0.157 is stated. In addition,

figure 3 shows a 2-year survival of 87.4% for the AVR >80 y group whereas in the text a 2-year survival of 89.7% is mentioned.

In our opinion comparison with a reference group should be handled with caution. We suggest the development of specific guidelines to compare an accurately matched population to ensure that all factors are taken into account and the comparison performed is methodologically correct.

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CHAPTER 23

Impact of Methodology and Assumptions in a Cost-Effectiveness Analysis on Transcatheter Aortic Valve Replacement

Osnabrugge RL, Kappetein AP.

J Thorac Cardiovasc Surg. 2013;145:607.

TO THE EDITOR:

With great interest we read the article on cost-effectiveness of transcatheter aortic valve implantation (TAVI) by Doble and colleagues in a recent issue of the *Journal*.[1] We congratulate the authors on their well-designed analysis of this timely and important topic. The investigators reported a base-case incremental cost-effectiveness ratio (ICER) of $51,324/quality-adjusted life-year (QALY) for TAVI versus standard management (SM) in surgically inoperable patients. In high-risk patients TAVI was economically dominated by surgical aortic valve replacement (SAVR). They concluded that TAVI is a cost-effective treatment option for inoperable patients, but not for high-risk patients. However, some methodological issues and questionable assumptions influence the outcomes.

The quality-of-life utilities were based on a conversion of New York Heart Association function classes, although direct EQ-5D utilities from the PARTNER trial have been available since the presentation at TransCatheter Therapeutics, November 7 2011, in San Francisco.[2] Moreover, TAVI via the transfemoral route is associated with improved quality-of-life compared to surgery, whereas this has not been demonstrated for the transapical route.[3] The authors lumped the quality-of-life improvement with these two distinct techniques together and reported 0.102 less QALYs after TAVI as compared with SAVR. This decrease is inconsistent with the quality-of-life results of transfemoral TAVI in the PARTNER trial and result in a too pessimistic ICER for TAVI versus SAVR in high-risk patients.

The authors used Canadian life tables to simulate long-term survival in all treatment groups, whereas a survival comparable to the general population is highly unlikely.[4] Table 2 shows that the method for extrapolating survival has a large influence on the ICER of TAVI versus SAVR.[1] A better approach would be to fit survival curves separately for the treatment groups using Weibull, log-normal and other models. In this way comorbidities such as diabetes mellitus, coronary artery disease, and prior myocardial infarction can be taken into account as covariables.

The inputs for the model came from a variety of sources and some assumptions are questionable. While unadjusted costs of balloon valvuloplasty were directly plugged in from a 23 year old study, figure 2 showed that these costs actually have a major influence on overall cost-effectiveness.[1] Also, the investigators used an excessive 36-day hospital stay after SAVR, and based the procedural costs of SAVR on septuagenarians instead of high-risk octogenarians. Furthermore, the short-term probability of acute kidney injury was estimated at 0.112, whereas 0.011 seems appropriate according to the PARTNER cohort B data.

The authors mentioned that the ICER of TAVI versus SAVR would be more favourable towards TAVI if the costs of the TAVI procedure had been lower. It would be interesting to report what the price of a TAVI valve would need to be in order to be a cost-effective alternative for SAVR.[5] Also, an elaboration on the differences with the PARTNER cost-effectiveness analyses would be valuable.

Methodology and assumptions influence the estimated outcomes in cost-effectiveness analyses. It would be interesting to see what the impact of our remarks would be on the cost-effectiveness estimates of TAVI in the current analysis.

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APPENDIX

Reply by Doble et al.

All properly conducted model-based economic evaluations should be a synthesis of best available evidence. It is important to note that economic models need to be updated once new evidence is available. The methods and assumptions used in our economic evaluation on transcatheter aortic valve implantation (TAVI) were appropriate because the evaluation was based on the best evidence available at the time of the analyses. Nevertheless, evidence on TAVI has grown rapidly in the past 2 years. We appreciate the comments raised by Osnabrugge and Kappetein and agree that a reexamination of the model with the new evidence is warranted.

Our analysis of TAVI compared with surgical aortic valve replacement (SAVR) grouped the patients undergoing transfemoral (TF) or transapical (TA) approach into 1 treatment arm. The reported clinical data from the Placement of Aortic Transcatheter Valve (PARTNER) cohort A also grouped these two different TAVI approaches to show the noninferiority of TAVI in terms of 1-year mortality. This was based on a sample size calculation of 650 patients at approximately 85% power.[1] The stratified clinical event rates provided in the Supplementary Appendix were not appropriate to use because of the lack of statistical power. It was estimated that 450 patients would need to undergo TF placement to show noninferiority of TAVI compared with SAVR at 85% power; however, only 244 patients were assigned to TF placement in the trial. It was therefore necessary to use utility values derived from the New York Heart Association functional classes, because this was the only relevant source that provided data for a similar patient population (i.e., patients undergoing TF and TA grouped together). Now that the full details of the PARTNER cohort A quality of life study are available,[2] we have imputed these EQ-5D utility values into our analysis (Table 1). TAVI was dominated by SAVR when using these EQ-5D utility values observed in both the TF and TA arms. TF compared with SAVR had an incremental cost-effectiveness ratio of $67,934/quality-adjusted life year (QALY) when the difference in utility values at years 2 to 20 of the model was assumed to be 0.09 in favor of TF.

The evidence on the long-term survival of patients undergoing TAVI is not available. Therefore, in the model, we directly used the mortality observed in the PARTNER trial for the first year and the mortality of the general public for the subsequent years. However, this approach does not imply that the survivals predicted by the model are comparable to those of the general public as argued by Osnabrugge and Kappetein. There were other mortalities caused by stroke, myocardial infarction, and acute kidney injury considered throughout the time horizon. We believe this is a reasonable approach to predict the survivals for the patient population. Of note, this base-case analysis was also supple-

Table 1.One-way sensitivity analysis of various model parameters

	TAVI vs SAVR	TAVI vs SM
PARTNER EQ-5D values		
Base case (NYHA converted to EQ-5D utilities)	Dominated	$51,324/QALY
EQ-5D utilities from the TF arm	Dominated*	$46,701/QALY†
EQ-5D utilities from the TF arm (assume 0.03 difference at ≥ 2 y)	$13,031,292/QALY	NA
EQ-5D utilities from the TF arm (assume 0.06 difference at ≥ 2 y)	$135,163/QALY	NA
EQ-5D utilities from the TF arm (assume 0.09 difference at ≥ 2 y)	$67,934/QALY	NA
EQ-5D utilities from the TA arm	Dominated	NA
Cost of balloon valvuloplasty		
Base case ($29,600)	NA	$51,324/QALY
$15,000	NA	$75,473/QALY
$20,000	NA	$67,203/QALY
$25,000	NA	$58,933/QALY
$30,000	NA	$50,662/QALY
$35,000	NA	$42,392/QALY
$40,000	NA	$34,121/QALY
Length of stay after SAVR		
Base case (36 d)	Dominated	NA
10 d	Dominated	NA
15 d	Dominated	NA
20 d	Dominated	NA
25 d	Dominated	NA
30 d	Dominated	NA
35 d	Dominated	NA
40 d	Dominated	NA
Procedural cost of SAVR		
Base case ($32,784)	Dominated	NA
$25,000	Dominated	NA
$30,000	Dominated	NA
$35,000	Dominated	NA
$40,000	Dominated	NA
$45,000	TAVI costs $1063 less at 0.102 less QALYs	NA
$50,000	TAVI costs $6063 less at 0.102 less QALYs	NA
Cost of TAVR valve		
Base case ($39,796)	Dominated	$51,324/QALY
$15,000	TAVI costs $13,642 less at 0.102 less QALYs	$10,310/QALY
$20,000	TAVI costs $8642 less at 0.102 less QALYs	$18,580/QALY
$25,000	TAVI costs $3642 less at 0.102 less QALYs	$26,851/QALY
$30,000	Dominated	$35,121/QALY
$35,000	Dominated	$43,391/QALY
$40,000	Dominated	$51,662/QALY
$45,000	Dominated	$59,932/QALY

NA, Not available; *NYHA,* New York Heart Association; *PARTNER,* Placement of Aortic Transcatheter Valve; *QALY,* quality-adjusted life year; *SAVR,* surgical aortic valve replacement; *SM,* standard management; *TA,* transapical; *TAVI,* transcatheter aortic valve implantation; *TF,* transfemoral.

* Difference in EQ-5D utility score at 1 year was equal to 0.01 as reported by Reynolds et al.[2]

† Utilities values for TF placement in inoperable patients obtained from Neyt and Van Brabandt.[3]

mented by the scenario analyses with different mortality assumptions. As suggested by Osnabrugge and Kappetein, the use of survival functions to fit patient-level data is another approach. This approach is obviously conditional on the access to patient-level data and is also subject to criticism. If there was any mortality benefit from TAVI observed at the end of the trial, the use of fitted survival functions is likely to enlarge the difference in favor of TAVI.[3]

Osnabrugge and Kappetein also were concerned about some resource use and cost inputs in the model. To address these concerns, we updated our 1-way sensitivity analyses (Table 1). Increasing the cost of balloon valvuloplasty improved the cost-effectiveness of TAVI, whereas changes in the length of hospital stay after SAVR had no impact. At high SAVR procedural costs or lower TAVI valve costs, TAVI gained less QALYs at lower costs compared with SAVR. The short-term probability of acute kidney injury was incorrectly listed in Table 1 of our original article, and the correct value of 0.011 was used in our model.

The trial-based economic evaluation by the PARTNER investigators used patient-level data to estimate the cost-effectiveness of TAVR compared with standard therapy from a US perspective.[4] Detailed costing was performed at an individual level using hospital-billing data. This is in contrast to the estimation of costs in our model, which were mainly based on average costs of long-term complication health states and may account for the difference in lifetime costs observed (incremental cost of $79,837 and $31,029, respectively). Larger values for incremental life-years (LYs) and QALYs (1.6 LYs and 1.3 QALYs compared with 0.9 LYs and 0.6 QALYs in our analysis) can be accounted for by the use of exponential models for survival extrapolation and a lower discount rate of 3% compared with 5% used in our model. Consequently, overall results were more favorable in our analysis with a reported incremental cost-effectiveness ratio of $51,324/QALY compared with $61,889/QALY in the trial-based analysis.

A comparison of the results from our cohort A analysis and that presented by Reynolds[5] at the TransCatheter Therapeutic conference is limited by the fact that the analysis by Reynolds was a trial-based approach using only 12 months follow-up and thus may not have captured all of the long-term costs and benefits of TAVR and SAVR. It will be important for Reynolds to model the lifetime effects of these two comparators to obtain more reliable estimates of cost-effectiveness.

Despite extensive review by an expert advisory panel and subsequent approval by the Food and Drug Administration, the appropriate use of the SAPIEN (Edwards Lifesciences, Irvine, CA) heart valve for high-risk operable patients remains uncertain. Unfortunately, uncertainty surrounding the benefits and risks of TAVI largely affects estimates of the

incremental cost-effectiveness. Although recently available evidence has shed some light, uncertainty still remains significant.

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CHAPTER 24

Long-Term Survival of Young Patients with Coronary Artery Disease is Best realized through Surgical Revascularization with Mammary Arteries

Head SJ, Osnabrugge RL, Kappetein AP.

J Am Coll Cardiol. 2013;61:2312-3.

TO THE EDITOR:

In a recent issue of the *Journal*, Flather et al.[1] reported a subgroup analysis of individual patient data from 10 randomized trials comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for multivessel coronary disease. Their analysis showed that there was a significant treatment-by-age interaction for 10-year mortality ($p < 0.001$). Strikingly enough, in the youngest age group of patients ≤56.2 years old there was no difference in mortality (hazard ratio for PCI = 1.23; 95% CI 0.95-1.59), while the hazard ratio shifted towards a significant benefit of CABG over PCI in older patients ≥65.2 years old (hazard ratio = 0.79; 95% CI 0.67-0.94).

Although the data from these trials are compelling, they were not performed according to the 'all-comers' design and it is therefore likely that there was a severe selection bias in the inclusion of patients. Young patients were probably those with low lesion complexity and it is known that in these patients CABG does not offer a survival benefit.[2] In contrast, even though the results of this study suggest superiority of CABG over PCI in elderly patients, this is counterintuitive and these results may not be generalizable to the majority of patients requiring coronary revascularization. Those patients with a higher risk profile were excluded from randomization because of procedural risks associated with CABG.[3] The advantage of PCI in the elderly patients could therefore not be identified in this pooled analysis.

Furthermore, long-term survival of young patients with more complex coronary artery disease is best realized through surgical revascularization with a left internal mammary artery to the left anterior descending artery. This will optimize long-term survival due to excellent graft patency,[4] which is critical especially in young patients with a relatively long life expectancy. Young patients that undergo PCI will have a high risk of multiple repeat revascularizations and are susceptive to the associated procedural risks.

The ancillary benefit of PCI to be preferred over CABG is its lesser invasiveness and shorter initial hospitalization.[5] However, the short-term deterrence of CABG in younger, fitter patients is less due to lower complication rates and shorter length of stay and time needed to resume normal activities of daily living. The benefit of PCI over CABG in younger patients may therefore be small, while long-term efficacy is clearly superior in the majority of young patients. The treatment of choice in young patients should therefore preferable be CABG.

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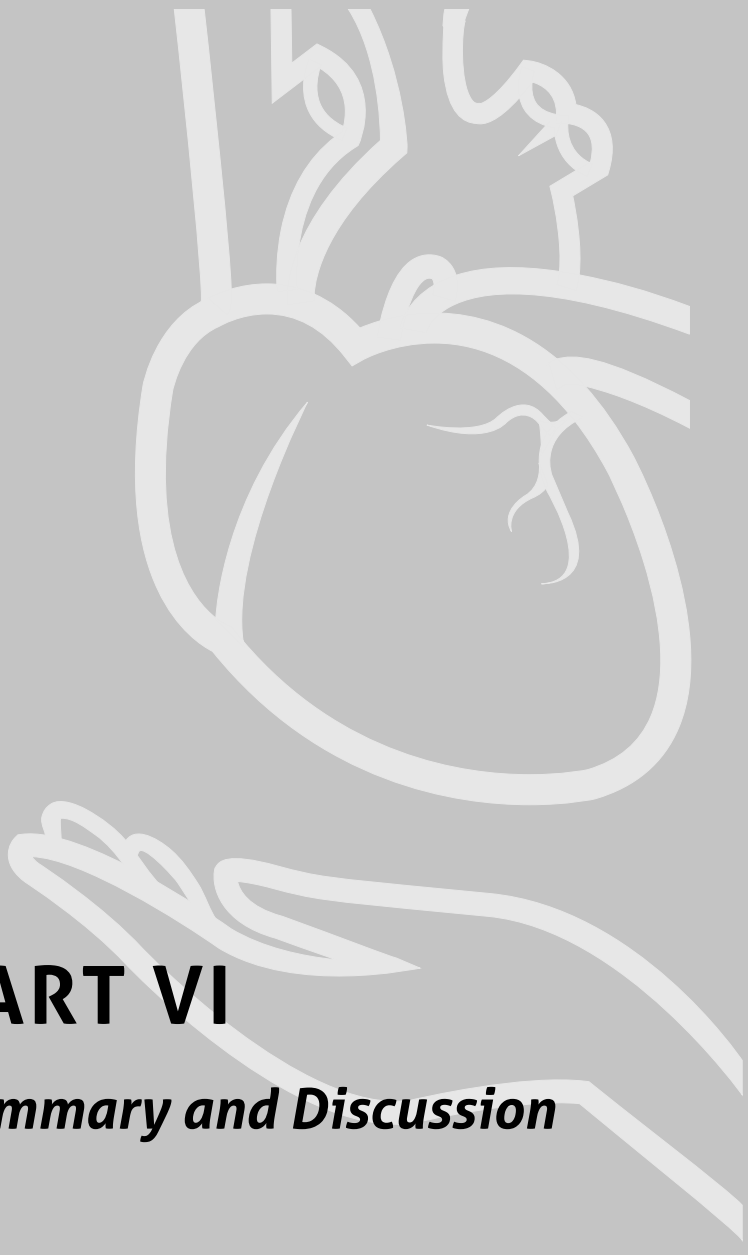

PART VI

Summary and Discussion

CHAPTER 25

Summary

PART I. INTRODUCTION

Chapter 1 is a general introduction to this thesis, describing the need for the combined evaluation of clinical outcomes, quality of life and costs in cardiovascular medicine. The aims and outline of this thesis are presented.

Chapter 2 introduces the reader to aortic stenosis and its considerable burden of disease. The treatment options surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) are introduced and the existing literature on the cost-effectiveness of TAVI is discussed. Despite underlying differences in methodology and healthcare systems across these studies, the relatively consistent results lead to the conclusion that TAVI is economically attractive when compared with medical management in patients who are not candidates for surgery. The cost-effectiveness analyses that compare TAVI and SAVR studies in patients at high operative risk draw markedly different conclusions on the economic attractiveness of TAVI in these patients. These differences largely depend on the cost input and the healthcare system in which the analysis is conducted.

Chapter 3 introduces alternative treatments for complex coronary artery disease. The most important clinical trials and large registries comparing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are discussed. In complex multi-vessel disease, CABG results in lower rates of long-term mortality, myocardial infarction and repeat revascularization when compared with PCI. These results are more pronounced in diabetics and in patients with lesions that are anatomically more complex. The application of the results of clinical trials may be limited due to restrictive eligibility criteria. Comparative effectiveness studies are, therefore, needed to complement the results of trials, but also have inherent limitations. Appropriate use criteria provide an important tool to measure how evidence from trials, large registries and guidelines is integrated in clinical practice. Decision-making is centered around heart team discussions and risk scores. Economic considerations will increasingly be included in decision-making, since the economic impact of ischemic heart disease is high and the growth of healthcare expenditure is unsustainable. In this context, the current studies show that CABG is associated with higher upfront costs, but is economically attractive at long-term follow-up.

PART II. AORTIC STENOSIS

In **Chapter 4** we study the disease prevalence of severe aortic stenosis and model the number of potential candidates for TAVI. A systematic search and meta-analysis show that the pooled prevalence of severe aortic stenosis in the elderly (>75 years old) is 3.4%. Using Monte Carlo simulations and literature searches of decision-making studies, we estimate that there are approximately 290,000 TAVI candidates under the current indications in North America and Europe. Annually, nearly 27,000 patients become eligible for TAVI.

In **Chapter 5** the adoption of TAVI in Western Europe is examined and factors that influence the heterogeneous utilization of this therapy are investigated. Between 2007 and 2011, more than 34,000 patients underwent TAVI in 11 European countries. There is wide variation in the number of TAVI implants per million individuals and penetration rates across countries. National economic indices and reimbursement strategies are closely linked with TAVI use and help explain the inequitable adoption.

Chapter 6 characterizes the health status outcomes for patients with severe aortic stenosis and extreme surgical risk who undergo TAVI with a self-expanding bioprosthesis. Given the advanced age and multiple comorbidities in these extreme risk patients, improvement in quality of life from the patient's perspective may be of even greater importance than prolonged survival. We show that TAVI is associated with substantial and meaningful improvement in both disease-specific and generic health status measures. However, there is a minority of patients who die or have very poor quality of life after TAVI. Baseline factors that are associated with poor outcome include measures of disability and frailty, comorbidities, and valve physiology.

The introduction of TAVI has led to more rigorous evaluation of SAVR as a benchmark for TAVI.

In **Chapter 7** the clinical outcomes, costs and resource use associated with SAVR in patients at different operating risk are evaluated. With increasing risk, the rates of post-operative mortality (low 1.2% vs. intermediate 2.7% vs. high 6.2%) and post-operative complications are higher. Similarly, length of stay and mean total costs increase according to risk category (low $35,021 vs. intermediate $46,101 vs. high $51,145). These data provide a basis for the evaluation of TAVI cost-effectiveness and its impact on the health care budget.

Chapter 8 compares the costs associated with TAVI and SAVR in patients at intermediate operating risk. In a propensity-matched analysis, the in-hospital costs are higher in TAVI patients than in SAVR patients (€40,902 vs. €33,354, respectively; $p = 0.010$). At one year

the difference in total costs persists (€46,217 vs. €35,511, respectively; $p = 0.009$). The difference is mainly caused by the higher costs of the transcatheter valve and is not compensated by the lower costs for blood products and hospital stay in TAVI patients.

Chapter 9 is a letter to the editor that adds to the discussion on the evidence base for the use of TAVI. Methodological comments on the most important TAVI trials and insinuations towards trial investigators are put into perspective.

Chapter 10 discusses the impact of severe aortic stenosis in patients requiring non-cardiac surgery. Commenting on a large study, we suggest that the better than anticipated outcomes imply that the threshold to proceed with the non-cardiac surgical procedure could be lowered. In symptomatic patients with severe aortic stenosis, however, non-cardiac surgery should be postponed until the aortic stenosis is treated with either TAVI or SAVR.

PART III. CORONARY REVASCULARIZATION

In **Chapter 11** the long-term clinical benefits and cost-effectiveness of CABG and PCI with drug-eluting stents (DES) are studied from a U.S. health care perspective. The total hospitalization costs are higher with CABG, but over the next 5 years, follow-up costs are higher with DES-PCI due to more frequent hospitalizations, repeat revascularization procedures, and higher medication costs. When extended to a lifetime horizon using a modeling approach, CABG is a clinically and economically attractive revascularization strategy compared with DES-PCI for patients with 3-vessel or left main coronary artery disease. However, among patients with less complex disease, DES-PCI may be preferred on both clinical and economic grounds.

In **Chapter 12**, the European perspective is applied on the lifetime cost-effectiveness of CABG versus DES-PCI. Moreover, the discriminative power of the SYNTAX Score II is assessed. This score is an individualised decision-making tool weighing anatomical and clinical factors to establish the optimal revascularisation strategy for patients with complex coronary artery disease. Despite differences in costs, utilities and lifetime extrapolation methodology, the overall results are comparable to those in Chapter 12. The SYNTAX Score II allows for objective decision-making between CABG and PCI, and also discriminates economic outcomes adequately.

Chapter 13 studies the impact of patient characteristics, comorbidities and complications on post-operative length of stay and total costs. Compared with post-operative

complications, patient characteristics have little impact on length of stay and costs. Upon validation, the models that combine pre- and post-operative variables explain variance better and are better calibrated than the pre-operative models. The pre-operative models are useful for prediction of costs and length of stay for groups of patients, case-mix adjustment in hospital benchmarking and pay-for-performance measures. The combined models identify incremental costs associated with complications and can be used for prioritizing quality improvement efforts.

In **Chapter 14**, value in CABG is defined and a framework to identify high-value centers is provided. Risk-adjusted length of stay and risk-adjusted morbidity/mortality are important outcome measures for assessing value in cardiac surgery. The proposed framework can be used to determine value in CABG, and identify high-value centers. This provides important information for quality improvement and pay-for-performance initiatives.

Chapter 15 discusses appropriate use criteria. These criteria integrate guidelines, clinical trial evidence, and expert opinion in order to determine the most appropriate care for a range of distinct clinical scenarios. Approximately 12-14% of all PCI and 1-2% of all CABG procedures in patients with stable angina are deemed inappropriate. Several reasons for this difference are identified. Continuous improvement of the criteria, multidisciplinary discussions, and the correct financial incentives will be essential in reducing the number of inappropriate procedures, improve patient outcomes, and contain costs.

PART IV. RISK PREDICTION IN CARDIAC SURGERY

Chapter 16 presents a validation study comparing the performance of two risk prediction models: the European System for Cardiac Operative Evaluation II (EuroSCORE II) versus the U.S. Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM). In a large U.S. multicenter database, the STS-PROM performs better than EuroSCORE II for CABG. However, the EuroSCORE II is a reasonable alternative in low-risk CABG patients and in those undergoing other cardiac surgical procedures. Due to overprediction of mortality, TAVI trials that use these scores for patient selection are enrolling patients that are at lower risk than anticipated.

Chapter 17 is a systematic review of risk prediction in adult cardiac surgery. Using an elaborate systematic literature search, we identify an extensive set of risk factors that are predictive of mortality, stroke, renal failure and/or length of stay after adult cardiac surgery. Current and future databases should consider collecting these variables in order to develop improved risk models.

Chapter 18 is a commentary on a strategic decision-support tool that predicts individual long-term survival (1, 5, and 10 years) after PCI with bare metal stents, after PCI with DES, and after CABG. These models help physicians to make recommendations, but a heart team approach to further individualize treatment is needed to ensure that every patient receives the optimal therapy.

PART V. METHODOLOGICAL APPRAISAL OF CARDIOVASCULAR RESEARCH

Chapter 19 is a letter to the editor about a meta-analysis. The letter highlights two methodological issues that hamper the interpretation of the association between *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel. First, the authors used an inappropriate strategy to reduce substantial heterogeneity in the results. Secondly, there was no assessment of potential bias that may have had impact on their results.

Chapter 20 systematically investigates how 11 overlapping meta-analyses on the association between *CYP2C19* loss-of-function alleles and clinical efficacy of clopidogrel could yield contradictory outcomes. The results of the meta-analyses differ because more recent meta-analyses included more primary studies and some had not included conference abstracts. Conclusions differ because between-study heterogeneity and publication bias were handled differently across meta-analyses. The substantial heterogeneity and publication bias implies that personalized antiplatelet management based on genotyping is not supported by the currently available evidence.

Chapter 21 evaluates the enormous increase in the number of meta-analyses in the cardiovascular field. This trend entails the publication of duplicate meta-analyses on the same topic. Although some replication of research is generally warranted, a large number of overlapping (discordant) meta-analyses reflects waste of resources, adds confusion to the field and threatens the value of the study design. Considerations regarding heterogeneity, publication bias and quality of primary studies should serve as a basis to appraise the evidence across overlapping meta-analyses. To maintain the appreciation of meta-analyses as the highest level of evidence, authors should adhere to the appropriate reporting guideline, describe the rationale for performing the (updated) meta-analysis, register their project in a dedicated database and evaluate the whole body of evidence.

Chapter 22 is a letter to the editor that stresses the importance of correctly comparing the survival of a specific patient population (patients undergoing SAVR) with that of the general population.

Chapter 23 is a letter to the editor on the impact of methodology and assumptions on the cost-effectiveness results for TAVI. The methodology for modeling utilities, extrapolating survival and the assumptions for model inputs influence the outcome of cost-effectiveness analyses.

Chapter 24 discusses the generalizability and interpretation of the results of a patient-level meta-analysis comparing CABG and PCI across different age categories.

CHAPTER 26

General Discussion

The aim of this thesis was to study the clinical, economic, and quality of life considerations for clinical decision-making and policy development in cardiovascular interventions for aortic stenosis and coronary artery disease. In this discussion chapter, the results will be put in a broader perspective, highlighting the implications for clinical decision-making and policy development. In addition, future developments will be discussed.

AORTIC STENOSIS (PART II)

In the field of structural heart disease, aortic stenosis is the most common valvular problem and its burden is expected to increase as the population is aging.[1] Surgical aortic valve replacement (SAVR) used to be the only treatment option, but now safe and reliable catheter-based techniques have emerged.[2-4] In patients with severe aortic stenosis who are not suitable candidates for surgery, transcatheter aortic valve implantation (TAVI) has been shown to result in substantial reductions in mortality (30.7% in the TAVI group versus 50.7% in the standard therapy group at 1 year).[3] Moreover, in patients at high surgical risk, TAVI was non-inferior to SAVR. Recently, the CoreValve US pivotal trial was the first randomized comparison showing that TAVI with a self-expandable valve resulted in higher one year survival compared to SAVR in patients at increased surgical risk.[5]

Disease Prevalence and Number of Candidates for TAVI

Since statistics on potentially treatable patients were only scarcely available, we conducted a systematic review and meta-analysis on the prevalence of aortic stenosis and estimated the number of candidates that are potentially treatable with TAVI (**Chapter 4**). Before this study, the prevalence of severe aortic stenosis in the elderly population was not clear as studies were scarce and reported disparate results. We found that the prevalence of severe aortic stenosis in the elderly was 3.4%. Although the studies differed with regard to the definition and severity of aortic stenosis, our finding relies on consistent estimations across studies. We also found that on average as many as 40.5% of patients with symptomatic severe aortic stenosis were not treated surgically. While the included studies differ with regard to the time period and degree of symptoms and stenosis, the analysis is the first to systematically assess this across studies, and stresses the undertreatment of patients with AS at high-operating risk.[6, 7]

Using population estimates and the estimates on decision-making in patients with aortic stenosis, we projected that currently almost 300,000 patients are candidates for TAVI in the US and Europe combined. Moreover, nearly 27,000 patients become eligible for TAVI annually. As a result of the heterogeneity of the underlying studies, these estimates are not exact and come with large confidence intervals. Nevertheless, our study was the

first to systematically project the number of potential TAVI candidates and provide some insights on the market size for these new devices.

TAVI Adoption and Policies for the Introduction of New Medical Technologies

Besides clinical evidence and costs, there are several other factors that determine the adoption of novel technologies like TAVI. In **Chapter 5** the actual number of TAVI implants across Europe is described, and a significant correlation between healthcare spending per capita and TAVI use was found. Moreover, countries with TAVI-specific reimbursement systems had more implants than countries that used restricted systems. While this was the first study to correlate TAVI adoption with economic indicators, the relationship was also seen for implantable cardiac defibrillators.[8] Economic prosperity and reimbursement seem to drive clinical practice.

Also, the review processes of new medical devices differ widely among countries. In the United States (U.S.) the Food and Drug Association (FDA) require clinical studies evaluating the safety and effectiveness of a high risk device as TAVI.[9] In Europe, devices require a Conformité Européenne (CE) mark that indicates market approval throughout the European Union (E.U.). The specific requirements for the CE mark are vague, but are usually met when the device is manufactured using a technically correct method. Moreover, it should perform as intended in a way that the benefits outweigh the expected risks and is followed by postmarketing surveillance.[9] The CE marking takes one to three months, whereas the average review time for high risk devices is 21 months in the U.S. In summary, the requirements in the E.U. are more easily met, since less rigorous proof of effectiveness is required. As a consequence, patients within the E.U. have faster access to new medical devices such as TAVI, but have a greater chance of later-identified adverse events. On the contrary, once approval has been given, the U.S. are quicker to arrange insurance coverage of the newly approved device.[10]

Risk Models and Decision-Making in Aortic Stenosis

Patient selection is important both for research purposes and clinical decision-making. To facilitate the process, several surgical risk scores are available to estimate the risk of perioperative mortality after aortic valve surgery. These scores are also used for patients undergoing TAVI. We show in **Chapter 16** that both the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) and EuroSCORE II significantly overpredict mortality in patients who are potentially treatable with TAVI. Consequently, patients selected for TAVI may be at lower risk than anticipated based on these scores. Instead, a dedicated risk model for TAVI should be developed from a large and uniform multicenter database.[11] Variables that would have to be considered include vessel tortuosity, frailty, access-site characteristics and angles of the aortic arch.

The patients' risk score should be combined with clinical judgment in a multidisciplinary heart team. After its first application in the SYNTAX trial for the discussion on the optimal revascularization therapy, the heart team concept has become a cornerstone in cardiovascular clinical decision-making.[12, 13] A valvular heart team should include a cardiac surgeon, an (interventional) cardiologist, an imaging specialist, a heart failure specialist, a cardiac rehabilitation specialist and a nurse practitioner. All relevant risk scores and additional information should be discussed and, with all the specialties aboard, they are more likely to come to a consensus on the optimal treatment for the patient at hand.

Quality of Life Considerations

Given the advanced age and multiple comorbidities in patients undergoing TAVI, improvement in quality of life from the patient's perspective may be of even greater importance than prolonged survival. We found that TAVI using a self-expanding bioprosthesis in patients at extreme operating risk is associated with substantial and meaningful improvement in both disease-specific and generic health status measures (**Chapter 6**). The study thus confirms that the health status benefits of TAVI are not restricted solely to balloon-expandable transcatheter valves,[14, 15] but also apply to the CoreValve self-expanding transcatheter valve.

Nevertheless, we found that almost 40% of the patients did not experience meaningful improvement in health status or survival at 6 months. Several factors, including comorbid conditions, disability/frailty, and valve physiology, were independently associated with poor outcomes after TAVI. One other study investigated predictors of poor outcome after TAVI, with a large overlap in predictors.[16] Further studies are required to determine a model that can be used prospectively to distinguish patients who are likely to benefit from TAVI from those for whom TAVI is futile. Being able to select the right patients will help obtain the best results, both from a clinical and economic perspective.

Costs and Cost-Effectiveness

The estimated large number of potential TAVI candidates has clinical, economic and social implications. Given the considerable costs of implanting TAVIs,[17] as well as the large and growing population of potential candidates, it is clear that not only clinical but also careful economic evaluation is required. The estimation of health care costs is based on the resources used by a health intervention and should be valued at its opportunity costs.[18] The measurement of opportunity costs are often expressed as market prices, since prices in competitive markets reflect the opportunity costs of resources. However, health care charges do not necessarily reflect market prices due to market distortions caused by e.g. health insurance, hospital accounting systems, and pricing policies. Therefore, adjust-

ments such as cost-to-charge ratios are applied and/or a micro-costing approach should be employed.

Both cost-to-charges on hospital billing data (**Chapter 7**) and micro-costing (**Chapter 8**) were applied in this thesis in order to estimate the costs associated with TAVI and SAVR. In **Chapter 7** we found that the cost of high-risk SAVR, based on adjusted hospital bills, are lower than the costs of SAVR in a randomized trial that combined resource-based accounting and hospital bills to estimate the cost-effectiveness of TAVI.[17] Our results suggest that in everyday practice TAVI is less likely to be an economically attractive treatment compared to SAVR than in the setting of a clinical trial. Another reason for the disparity in costs might be that the randomized trial included only 12% of the screened severe aortic stenosis patients, thereby limiting the generalizability of its clinical and economic results. However, a direct comparison across studies should always be considered exploratory. In **Chapter 8** we applied micro-costing to compare the direct hospital costs and one-year follow-up costs of TAVI versus SAVR in a propensity matched cohort of patients at intermediate operating risk. It is the first and currently only study with a detailed focus on costs in this patient category. Importantly, the four times higher costs of materials in TAVI were not compensated by lower costs of blood products and length of stay. It is important to note however that the TAVI patients in this study reflect relatively early experience and that market forces are likely to decrease the price of transcatheter valves (currently almost €18,000) as more valves enter the market. Still, with approximately €10,000 higher costs after TAVI at one year, it will be interesting to see what the quality of life results of ongoing randomized studies will show in patients at intermediate operating risk. These results are important for the cost-effectiveness and accompanying economic attractiveness of TAVI in those patients.

Future Developments influencing Cost-Effectiveness

Several factors and developments are likely to influence the cost-effectiveness of TAVI compared with SAVR in the future. First, there are currently no long-term follow-up data regarding TAVI durability. Although the biomaterials comprising current transcatheter valves are quite similar to those of current surgical bioprostheses, it is unknown whether the process of crimping and valve deployment might have a harmful effect on the long-term integrity of the valve that could result in higher rates of structural valve deterioration and late reoperation, particularly as TAVI is performed in younger and lower risk individuals. Although studies have yet to address these issues explicitly, it is intuitive that the additional costs, complications, and quality of life reductions associated with premature valve failure would reduce the cost-effectiveness of TAVI compared with SAVR.

The costs of the TAVI procedure and hospitalization are also likely to evolve over the next several years. For example, as more manufacturers enter the TAVI market, it is expected that the price of transcatheter valves will drop, making TAVI more cost-effective compared with current levels. Length-of stay is another important driver influencing both the cost and cost-effectiveness of TAVI. Although TAVI is less invasive than SAVR, the mean length of stay after TAVI among truly high risk patients was 10 days in the Placement of AoRTic TraNscathetER Valves (PARTNER) A trial (16 days among patients treated via the transapical approach) and 11 in our study of intermediate risk patients (**Chapter 8**).[14, 17] As device profiles continue to decrease and operator experience grows, it can be expected that length of stay for TAVI will decrease, which should also favorably impact the cost-effectiveness of TAVI relative to SAVR. SAVR, on the other hand, is a relatively mature procedure that is unlikely to achieve comparable length of stay reductions.

Recently, it was shown that TAVI resulted in better one year survival compared to SAVR in patients at increased surgical risk,[5] and now the ongoing SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) and PARTNER II trials will compare TAVI versus SAVR in even lower risk patients. In **Chapter 4** we estimated that a further 145,000 patients would become TAVI eligible when these trials show favorable results for TAVI. If in the future, TAVI will show good safety and effectiveness compared to SAVR in even low risk patients, another 730,000 patients in the U.S. and Europe would become TAVI eligible. Given the size of these numbers and the costs associated with TAVI, demonstrating both economic and quality of life benefits will be an important goal of randomized trials in order to justify expansion of TAVI indications into such lower risk patients.

Of note, only the U.S. perspective PARTNER trial has specifically captured the cost of high-risk SAVR in patients who would otherwise be considered for TAVI. The rapid acceptance and proliferation of TAVI for high risk patients (and even intermediate risk patients) in many European countries has made randomized trials challenging in those settings—leaving unanswered questions about the costs and outcomes of SAVR in truly high risk individuals.

Finally, it is important to recognize that whether TAVI is truly 'cost-effective' depends on a society's ability and willingness-to-pay for health benefits.[19] The World Health Organization applies a threshold of three times the gross domestic product (GDP). Thus, an incremental cost-effectiveness ratio of $50,000/QALY or €30,000/QALY gained may be acceptable in the United States or relatively wealthy countries in Western Europe, but is likely to far exceed the societal threshold in less developed societies where the cost-effectiveness threshold may be <$10,000/QALY gained.

CORONARY REVASCULARIZATION (PART III)

Compared with TAVI, the catheter-based technique for the treatment of coronary artery disease is more mature. Since Andreas Grüntzig performed the first percutaneous coronary intervention (PCI) in 1977,[20] millions of patients have undergone this procedure, and it has been compared extensively versus medical therapy and versus coronary artery bypass grafting (CABG) (**Chapter 3**). The Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial is the most contemporary trial to compare PCI with drug-eluting stents (DES-PCI) versus CABG in patients with 3-vessel or left main disease. At 5-year follow-up, CABG was associated with a lower rate of the composite endpoint (cardiovascular death, myocardial infarction, stroke, or repeat revascularization) compared with DES-PCI.[21] The difference was predominantly driven by reductions in non-fatal myocardial infarction and repeat revascularization. However, DES-PCI was associated with a lower rate of stroke in the overall population, and DES-PCI is a reasonable alternative in subgroups of patients with anatomically less complex disease (low SYNTAX score), or left main coronary artery disease.[21]

Cost-Effectiveness Results

Procedures for coronary revascularization account for nearly $12 billion/year in direct costs alone, and virtually all healthcare systems are faced by economic challenges. Therefore, it is critical that the alternative revascularization procedures PCI and CABG are not only compared clinically but also economically. In this thesis, the long-term cost-effectiveness and clinical benefits of DES-PCI versus CABG were described for patients with 3-vessel or left main coronary artery disease from a U.S. (**Chapter 11**) and Dutch perspective (**Chapter 12**). The initial hospitalization costs were higher with CABG, but during the 5-year follow-up the costs were higher with DES-PCI due to more frequent repeat revascularization procedures, hospitalizations, and higher costs for medication. Using a modeling approach to extend the trial results to a lifetime horizon, CABG was a clinically and economically attractive revascularization strategy compared with DES-PCI in these patients. However, among patients with anatomically less complex disease, DES-PCI may be preferred, both from a clinical and economic perspective.

Country-Specificity of Cost-Effectiveness Results

Results from cost-effectiveness analyses differ among countries for many reasons, including the epidemiological context, health care system characteristics, clinical practice patterns, severity of disease and differences in prices for labor and resources. Even though the SYNTAX trial was conducted in 18 different countries, guidelines for cost-effectiveness studies recommend the application of country-specific costs.[22-24] In **Chapter 11** we applied the U.S. health care perspective, while in **Chapter 12**, we analyzed the

cost-effectiveness from a Dutch perspective. At the same time, the recommendations for economic analyses alongside multinational trials indicate that all the clinical outcomes can be assumed to be similar across countries.[25] Although costs, EQ-5D utilities and lifetime extrapolation methodology differed, the overall conclusions are comparable between the two chapters. In order to facilitate further comparison, we applied exchange rates and purchasing power parities (PPP). Small differences remained, which is likely the result of differences in utilities, practice patterns and the significantly higher health care prices in the U.S.[26] More importantly, PPP is a generic conversion factor based on generic goods and services. It is not specific for health care, let alone for specific procedures like coronary revascularization.[27] In short, the international transferability of cost-effectiveness evaluations is a field of debate,[28] and future studies are required to determine the optimal methodology for conducting economic analyses alongside multinational clinical trials.

Time Horizon

An important finding was that an appropriate time horizon should be used in cost-effectiveness analyses. Meaningful clinical differences between treatments might arise only after 3 years. A prior SYNTAX cost-effectiveness analysis based on the 1-year results showed totally different results. In contrast with the findings in **Chapters 11 and 12**, DES-PCI was the economically dominant treatment strategy.[29] The discrepancy emphasizes the importance of basing policy decisions on clinical trials with appropriate follow-up times.

Subgroup Analyses

An important finding of the SYNTAX trial was that the preferred treatment strategy depends on the anatomical complexity of the coronary lesions, as described by the SYNTAX Score.[21, 30] Although the overall long-term cost-effectiveness results in the SYNTAX trial were in favor of CABG, subgroup analyses showed that DES-PCI was favored in patients with low SYNTAX Scores, both from an economical and clinical perspective. In contrast, for patients with high SYNTAX Scores, CABG was strongly favored on economic grounds.

In **Chapter 12** we also analysed the economic implications of the SYNTAX Score II. This score was recently introduced to provide an impartial, evidence-based tool in the decision-making process for clinicians weighing clinical and anatomical factors to establish the optimal revascularization strategy for patients with complex coronary artery disease.[31] Similarly to the original SYNTAX Score, we showed that the new score is not only an excellent clinical risk stratifier, but also adequately discriminates economic outcomes. Although subgroup analyses are usually considered 'hypothesis-generating' in clinical trials, cost-effectiveness analysis is driven by absolute measures of cost and

benefits. Therefore, subgroup results in cost-effectiveness analyses are often considered to be valid for guideline development and healthcare policy, provided that the results are pathophysiologically plausible and supported by appropriate uncertainty analyses.[32]

New Developments influencing the Cost-Effectiveness of PCI versus CABG

In the rapidly moving field of PCI, there are several developments that have potential impact on the cost-effectiveness results of PCI versus CABG. First, second-generation DES have demonstrated lower rates of MI, target vessel revascularization, and stent thrombosis as compared with first-generation DES.[33] These developments are likely to enhance the economic profile of PCI in cost-effectiveness analyses. However, there is no evidence (yet) that this newer generation improves survival compared with earlier generations.

Moreover, continuous development and market dynamics are driving down the price of stents further. In **Chapter 11** and **Chapter 12** we showed that the results were only minimally sensitive to stent pricing. Although stent prices are frequently perceived to be a principal determinant of cost-effectiveness, the gain in life expectancy rather than stent price appears to be the major determinant. Finally, fractional flow reserve (FFR) guidance for PCI has shown to improve clinical outcomes and lower long-term costs compared with angiography-guided PCI.[34, 35] Future studies will have to determine the clinical and economic results of PCI with FFR versus CABG.

Resource Management and Policy Development

This thesis also provides tools that can be used for resource management and policy development for centers and surgeons that perform CABG. In **Chapter 13**, we provided models allowing hospital administrators, operating room managers, and cardiac surgeons to identify the implications and predictive power of patient characteristics, comorbidities, and complications on the resource use and costs of CABG. This information is useful in planning resource use and for prioritizing quality improvement efforts. In our models, patient characteristics and comorbidities explained only a small portion of length of stay and costs. Therefore, policy makers should first focus on reduction of complications. Frequent, high-cost complications were identified and should be the first focus of quality-improvement efforts.

Current health care policy measures such as pay-for-performance provide financial incentives to improve value (i.e. to keep costs low by improving outcomes and quality of care).[9, 36] In general, these measures provide incentives that inversely relate payment with risk-adjusted clinical outcomes and risk-adjusted resource use. The high annual volume and associated costs of CABG procedures make this type of surgery a natural target for cost containment and process improvement. **Chapter 14** is the first study to

apply the concept of value to a specific procedure (CABG). We found distinct variability in value when both risk-adjusted quality and cost measures were combined, but the exact definitions of low/high performers still require close collaboration with the physician community before changes in payments can be implemented. In addition, future studies should measure direct resource consumption per patient and apply standardized unit costs.[37] Nevertheless, our findings suggest that better quality leads to shorter postoperative length of stay and resource use. Substantial savings and improved outcomes can be realized if all centers achieve the same performance of high-value centers.

The reduction of waste, or not value-added care, is another focus in the quest for sustainable health care finances. The most conservative estimates show that approximately 20% of total health care expenditure in the U.S. consists of waste.[38] There are roughly six categories of waste in health care: failures of care delivery, failures of care coordination, overtreatment, administrative complexity, pricing failures, fraud and abuse. In **Chapter 15** we discuss the application of appropriate use criteria for coronary revascularization, which is related to three of these categories (failure of delivery, overtreatment, and fraud and abuse). If there is stricter application of guidelines and appropriate use criteria, patient outcomes will improve while costs are reduced.

RISK PREDICTION IN CARDIAC SURGERY (PART IV)

While Part III focused on the economic aspects in clinical decision-making, the expected risks and benefits in terms of survival are at least as important. To estimate the expected risks and benefits, several risk models are available, including the original EuroSCORE, EuroSCORE II, and the STS-PROM. In **Chapter 16**, we found that the STS-PROM was superior in identifying patients that were likely to survive cardiac surgery and was also better calibrated. The performance of the EuroSCORE was inadequate, whereas the EuroSCORE II performed satisfactorily, especially in recent low risk CABG and non-CABG procedures. In general, the models overpredict mortality, meaning that patients have lower operating risks than anticipated based on the scores.

There are several reasons why the STS-PROM performed better than the EuroSCORE II. The STS-PROM used a database containing >25 times more patients than the EuroSCORE II, and used more uniform definitions in the underlying database. On the other hand, the EuroSCORE II is easier to use as it only requires 18 variables compared to >40 variables in the STS-PROM model. **Chapter 16** also stresses the importance of frequently updating risk scores. Recent scores performed better in more recent validation cohorts. When updating and improving risk scores, the underlying database should be large and

also consider less common variables and outcomes other than mortality, including renal failure, stroke, and length of stay (**Chapter 17**). However, the added value of collecting this extra information needs to be weighed against the cost of collecting them.

Still, despite attempts to improve models by incorporating additional variables, there will always be factors that are not included, rendering the score suboptimal and not suitable for the individual patient. Therefore, risk scores are supplements to clinical judgment and serve as a starting point for multidisciplinary heart team discussions. The heart team itself should be reimbursed in order take financial incentives out of the clinical decision-making process.

METHODOLOGICAL APPRAISAL OF CARDIOVASCULAR RESEARCH (PART V)

The final chapters of this thesis accentuate the importance of methodological aspects in cardiovascular research. Increasingly, there is concern that most published research findings are false.[39] The concern is larger when studies and effect sizes are smaller; when the number of tested relationships is larger; when a variety in designs, definitions, outcomes and analytic methods is available; when there is greater financial or personal interest; and when more research teams are involved. Cardiovascular research regularly meets many of these criteria.

Methodological flaws in meta-analyses may influence the interpretation and clinical consequences of results. With the exciting promises of whole genome sequencing and its translation to health care practice, careful reporting and appraisal of evidence is crucial.[40] In **Chapter 19** we express our concerns regarding the methodology and interpretation of a meta-analysis on the association between *CYP2C19* loss-of-function alleles and the clinical efficacy of clopidogrel. The authors use an inappropriate strategy to reduce the substantial heterogeneity in the results and there was no assessment of potential bias. Distressingly, 10 other meta-analyses on the same topic also pay little attention to heterogeneity and publication bias (**Chapter 20**). Nevertheless, the substantial heterogeneity and publication bias found in the meta-analyses imply that personalized antiplatelet management based on genotyping is not supported by the currently available evidence. These methodological difficulties combined with the disproportionate increase in the number of (discordant) meta-analyses form the rationale behind the recommendations for the appraisal of meta-analyses in cardiovascular medicine (**Chapter 21**).

Methodological aspects also influence the validity of other study designs. For instance, when survival is incorrectly compared with a reference population, the effect of treat-

ment (SAVR) could be overestimated (**Chapter 22**). Cost-effectiveness analyses are in particular prone to assumptions with regard to model inputs and extrapolation techniques (**Chapter 23**).

The generalizability of results is a very important additional consideration when interpreting results of clinical trials. There is a subtle balance between the need for exclusion criteria to optimize internal validity and the need for less stringent criteria to determine an intervention's effectiveness in everyday clinical practice. **Chapter 24** explains that a remarkable finding may be the result of strict selection of patients in clinical trials. Such a selection bias limits the applicability of the results to everyday clinical practice and should be considered when interpreting the results. In summary, a continuous and sensible debate on the most appropriate methodology and critical appraisal of research should be the foundation for progress in the field of cardiovascular medicine.

CONCLUSIONS

The management of aortic stenosis and coronary artery disease are rapidly moving fields. In this thesis we showed updates of clinical, economic and quality of life aspects as treatment considerations in decision-making. Aortic stenosis will remain prevalent among the elderly. TAVI is a new and promising catheter-based technique in a world where treatments are increasingly performed less invasively. Since the majority of patients consists of the elderly, quality of life aspects may be even more important than increased survival. Also, specific models will help identifying patients that are most likely to benefit from the procedure, thereby enhancing the clinical and economic profile of TAVI. Due to the large (potentially) treatable patient population and the high costs associated with TAVI, economic comparisons with SAVR are warranted.

The high clinical and economic burden of coronary artery disease and soaring health care costs demand health economic analyses of CABG and PCI. CABG is a clinically and economically attractive revascularization strategy compared with DES-PCI in patients with 3-vessel or left main coronary artery disease. However, among patients with anatomically less complex disease, DES-PCI may be preferred, both from a clinical and economic perspective. The prediction of resource use, pay-for-performance measures and appropriate use criteria will lead to improved outcomes while reducing costs.

The performance of risk prediction models is suboptimal and not always suitable for the individual patient. Rather, multidisciplinary heart team discussion in which risk scores and clinical judgment are combined, should be the cornerstone of clinical decision-making.

Moreover, the critical appraisal of research and continuous debate on the best methodology should be the foundation for progress in the field of cardiovascular medicine.

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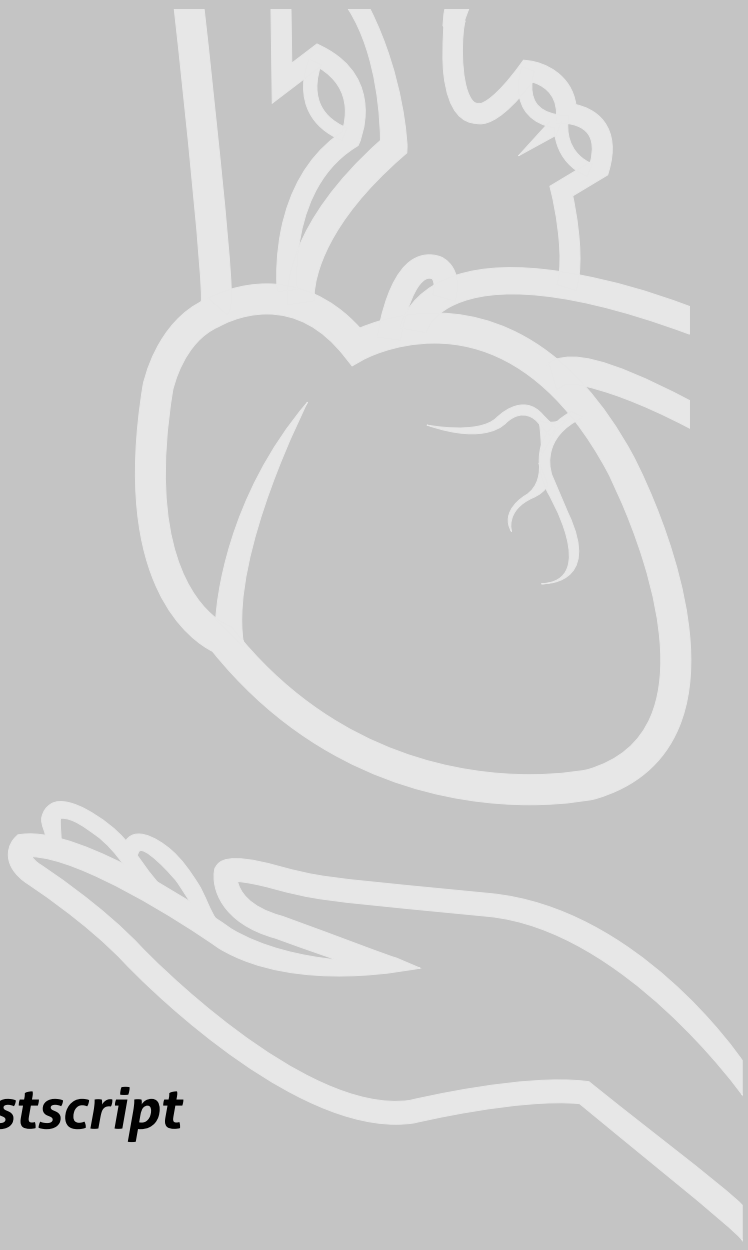

Postscript

CHAPTER 27

Nederlandstalige Samenvatting

DEEL I. INLEIDING

Hoofdstuk 1 is de algemene introductie waarin de beweegredenen worden beschreven voor de gecombineerde evaluatie van klinische uitkomsten, kwaliteit van leven en kosten in de cardiovasculaire geneeskunde. De doelen en onderzoeksvragen worden uiteengezet.

Hoofdstuk 2 introduceert de ziekte aortaklepstenose en de bijbehorende ziektelast. Chirurgische aortaklepvervanging (SAVR) en transkatheter aortaklepvervanging (TAVI) worden besproken en de bestaande literatuur over kosteneffectiviteit van TAVI wordt bediscussieerd. Ondanks verschillen in methodologie en zorgstelsels laten de resultaten van bestaande studies zien dat, voor patiënten die geen kandidaat zijn voor SAVR, TAVI economisch aantrekkelijk is wanneer het wordt vergeleken met medicamenteuze behandeling van aortaklepstenose. De conclusies van kosteneffectiviteitsanalyses die TAVI en SAVR vergeleken in patiënten met een hoog operatief risico, verschillen sterk. De verschillen worden met name veroorzaakt door verschillen in toegepaste kosten en het zorgstelsel waarin de analyse werd uitgevoerd.

Hoofdstuk 3 introduceert verschillende behandelingen voor complex coronairlijden. De belangrijkste *clinical trials* en *registries* die *coronary artery bypass graft* operaties (CABG) vergeleken met percutane coronaire interventies (PCI), worden besproken. In complex coronairlijden leidt CABG tot een lagere lange termijn mortaliteit, minder hartinfarcten en minder hernieuwde revascularisaties in vergelijking tot PCI. Deze verschillen in resultaten zijn sterker in diabetici en in patiënten met anatomisch meer complexe laesies. De toepasbaarheid van de resultaten van *clinical trials* op de klinische praktijk kan beperkt zijn vanwege restrictieve selectiecriteria van patiënten. *Comparative effectiveness studies* reflecteren de werkelijke klinische praktijk beter, maar kennen hun eigen beperkingen. Het hart team en risico voorspelmodellen zijn belangrijke aspecten van de klinische besluitvorming. Daarnaast worden economische afwegingen steeds belangrijker, vanwege de hoge economische impact van coronairlijden en de onhoudbare groei van de zorgkosten.

DEEL II. AORTAKLEPSTENOSE

In **Hoofdstuk 4** wordt de prevalentie van ernstige aortaklepstenose bestudeerd en wordt het aantal potentiële TAVI kandidaten gemodelleerd. Systematisch literatuuronderzoek en meta-analyse laat zien dat de prevalentie in bejaarde patiënten (>75 jaar oud) 3.4% was. Met behulp van Monte Carlo simulaties en literatuuronderzoek schatten we dat

er, onder de huidige indicaties, ongeveer 290.000 patiënten TAVI kunnen ondergaan in Noord-Amerika en Europa. Jaarlijks zijn er bijna 27.000 nieuwe TAVI patiënten.

In **Hoofdstuk 5** wordt de adoptie van TAVI in verschillende West-Europese landen bestudeerd, alsmede de factoren die van invloed zijn op verschil in gebruik van deze therapie. Tussen 2007 en 2011 ondergingen meer dan 34.000 patiënten een TAVI procedure in 11 Europese landen. Er zijn grote verschillen in het aantal TAVI implantaten per miljoen inwoners en de penetratie van TAVI tussen de landen. Indicatoren van de economie en vergoedingen zijn geassocieerd met TAVI gebruik en verklaren deels de ongelijke adoptie tussen landen.

Hoofdstuk 6 beschrijft de kwaliteit van leven van patiënten met ernstige aortaklepstenose die TAVI ondergaan met een *self-expanding* bioklepprothese. De patiënten hadden een extreem hoog operatief risico. Gezien de hoge leeftijd en verschillende comorbiditeiten in deze extreem hoog risico groep, kan vooruitgang in kwaliteit van leven hoger worden gewaardeerd dan verlengde levensduur. We laten zien dat TAVI is geassocieerd met substantiële, belangrijke vooruitgang in zowel ziekte-specifieke als algemene kwaliteit van leven. Invaliditeit, algehele zwakte, comorbiditeiten en klepfysiologie zijn belangrijke factoren die zijn geassocieerd met een slechte uitkomst na TAVI.

De introductie van TAVI heeft geleid tot een herevaluatie van SAVR als maatstaf waarmee TAVI wordt vergeleken.

In **Hoofdstuk 7** worden de klinische uitkomsten en kosten van SAVR in verschillende risico-categorieën geëvalueerd. Met toenemend risico, neemt de operatiesterfte (laag 1.2% vs. gemiddeld 2.7% vs. hoog 6.2%) en het aantal post-operatieve complicaties toe. Op eenzelfde manier nemen de ligduur en de gemiddelde totale kosten toe met het operatierisico (laag $35.021 vs. gemiddeld $46.101 vs. hoog $51.145). Deze data geven een maatstaf voor de evaluatie van de kosteneffectiviteit en economische impact van TAVI.

Hoofdstuk 8 vergelijkt de kosten van TAVI en SAVR in een groep patiënten met een gemiddeld operatie risico. In een *propensity-matched* analyse zijn de kosten in het ziekenhuis hoger in TAVI patiënten dan in SAVR patiënten (€40.902 vs. €33.354, $p = 0.010$). Ook na één jaar blijft dit verschil in kosten bestaan (€46.217 vs. €35.511, $p = 0.009$). Het verschil wordt met name veroorzaakt door de hogere kosten van de transkatheter klep en wordt niet gecompenseerd door de lagere kosten voor bloedproducten en ziekenhuisverblijf in de TAVI groep.

Hoofdstuk 9 is een brief aan de *editor* die bijdraagt aan de discussie over het bewijs voor de (kosten)effectiviteit van TAVI. Methodologisch commentaar op de belangrijkste TAVI trials en insinuaties richting hoofdonderzoekers van trials worden in perspectief gezet.

Hoofdstuk 10 bediscussieert de impact van ernstige aortaklepstenose in patiënten die een niet-hartchirurgische operatie ondergaan. In een commentaar op een grote studie, suggereren wij dat de buitengewoon goede resultaten impliceren dat de drempel om de niet-hartchirurgische operatie te ondergaan verlaagd kan worden. Echter, in patiënten met symptomatische ernstige aortaklepstenose moet de operatie worden uitgesteld totdat de aortaklepstenose is behandeld, danwel met TAVI of SAVR.

DEEL III. REVASCULARISATIE VAN DE CORONAIRARTERIËN

In **Hoofdstuk 11** worden de lange termijn klinische voordelen en kosteneffectiviteit van CABG en PCI met *drug-eluting stents* (DES) bestudeerd vanuit het perspectief van het Amerikaanse zorgsysteem. De totale kosten van het ziekenhuisverblijf zijn hoger met CABG, maar gedurende een 5-jarige follow-up zijn de kosten met DES-PCI hoger vanwege meer ziekenhuisopnames, hernieuwde revascularisaties en hogere medicatiekosten. Ook bij extrapolatie naar de resterende duur van de levens van de patiënten, blijkt CABG een klinisch en economisch aantrekkelijke revascularisatie strategie te zijn vergeleken met DES-PCI in patiënten met 3-vats- of hoofdstam coronairlijden. Echter, onder patiënten met minder complex coronairlijden is DES-PCI wellicht te prefereren, zowel vanuit klinisch als economisch perspectief.

In **Hoofdstuk 12** wordt de kosteneffectiviteit van CABG vs. DES-PCI bestudeerd vanuit een Europees perspectief. Bovendien wordt de discrimineerde kracht van de SYNTAX Score II geëvalueerd. Deze score is een geïndividualiseerde beslishulp die zowel anatomische als klinische factoren combineert om de optimale revascularisatie strategie te kiezen. Ondanks de verschillen in kosten, utiliteiten en extrapolatietechnieken, zijn de resultaten vergelijkbaar met die uit Hoofdstuk 12. De SYNTAX Score II is een geobjectiveerde beslishulp bij de keuze tussen CABG en PCI en blijkt ook economische uitkomsten goed te discrimineren.

Hoofdstuk 13 bestudeert de impact van patiëntkarakteristieken, comorbiditeiten en complicaties op de duur van het post-operatieve ziekenhuisverblijf en de daarbij behorende totale kosten. Vergeleken met post-operatieve complicaties hebben patiëntkarakteristieken weinig invloed op de totale verblijfsduur en kosten. Bij validatie blijkt dat modellen met zowel pre- als post-operatieve variabelen beter de variantie verklaren en beter zijn

gekalibreerd dan de modellen met louter pre-operatieve variabelen. De pre-operatieve modellen zijn nuttig om kosten en ligduur te voorspellen voor groepen van patiënten, vergelijkingen van ziekenhuisprestaties en uitkomstbekostiging. De gecombineerde modellen identificeren incrementele kosten geassocieerd met complicaties en kunnen worden gebruikt bij het prioriteren van initiatieven tot kwaliteitsverbetering.

In **Hoofdstuk 14** wordt gezocht naar een definitie van '*value*' van CABG procedures en wordt een raamwerk gepresenteerd waarmee centra met hoge 'waarde' kunnen worden geïdentificeerd. Risico-gewogen ligduur en risico-gewogen morbiditeit/mortaliteit zijn belangrijke uitkomstmaten om de '*value*' van CABG vast te stellen en goed presterende centra te identificeren. Deze data zijn belangrijk voor kwaliteitsverbetering en uitkomstbekostiging.

Hoofdstuk 15 bediscussieert criteria om de gepastheid van het uitvoeren van revascularisatie procedures te bepalen. Deze criteria maken gebruik van richtlijnen, *clinical trials*, en het oordeel van deskundigen om de meest gepaste zorg voor verschillende klinische scenario's vast te stellen. Ongeveer 12-14% van alle PCI en 1-2% van alle CABG procedures in patiënten met stabiele angina pectoris wordt als ongepast beoordeeld. Continue verbetering van de criteria, multidisciplinaire discussies en de juiste financiële prikkels zijn essentieel bij het terugdringen van het aantal ongepaste revascularisatie procedures, het verbeteren van uitkomsten en het beheersen van kosten.

DEEL IV. VOORSPELLEN VAN RISICO BINNEN DE HARTCHIRURGIE

Hoofdstuk 16 vergelijkt de prestaties van twee risico voorspelmodellen: het *European System for Cardiac Operative Evaluation II* (EuroSCORE II) wordt gevalideerd en vergeleken met de Amerikaanse Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM). In een grote Amerikaanse multicenter database presteert de STS-PROM beter dan de EuroSCORE II voor patiënten die CABG ondergaan. De EuroSCORE II is echter een billijk alternatief voor CABG patiënten met een laag operatierisico en voor patiënten die een andere hartchirurgische ingreep ondergaan. De mortaliteit wordt door beide modellen overschat in patiënten met aortaklepstenose. Daardoor includeren TAVI studies die met behulp van deze modellen patiënten selecteren eigenlijk patiënten met een lager risicoprofiel dan was voorzien.

Hoofdstuk 17 is een systematische review van risicopredictie binnen de hartchirurgie. Met behulp van een uitgebreide systematische literatuurstudie identificeren we een groot aantal risicofactoren die voorspellende waarde hebben voor mortaliteit, cerebro-

vasculaire accidenten, nierfalen en/of ligduur na een hartchirurgische ingreep. Huidige en toekomstige databases zouden het verzamelen van de geïdentificeerde variabelen moeten overwegen zodat in de toekomst verbeterde risicomodellen ontwikkeld kunnen worden.

Hoofdstuk 18 is een commentaar op een besliskundig model dat individuele lange termijn overleving (1, 5, en 10 jaar) voorspelt na PCI met *bare metal stents*, na DES-PCI, en na CABG. Deze modellen helpen artsen bij het aanbevelen van de te kiezen behandelmethode. Een multidisciplinair hart team blijft echter de hoeksteen van het besluitvormingsproces.

DEEL V. METHODOLOGISCHE EVALUATIE VAN CARDIOVASCULAIR ONDERZOEK

Hoofdstuk 19 is een brief aan de *editor* over een meta-analyse. In de brief worden twee methodologische kwesties kritisch beschouwd die de associatie tussen *CYP2C19 loss-of-function* allelen en klinische effectiviteit van clopidogrel verstoren. Ten eerste gebruiken de auteurs een ongeschikte methode om de substantiële heterogeniteit te verminderen. Ten tweede werd *publication bias* niet onderzocht, hoewel deze de resultaten weldegelijk kan hebben beïnvloed.

Hoofdstuk 20 onderzoekt op een systematische manier hoe 11 overlappende meta-analyses tegenstrijdige resultaten konden opleveren ten aanzien van de associatie tussen *CYP2C19 loss-of-function* allelen en de klinische effectiviteit van clopidogrel. De resultaten van de meta-analyses verschillen omdat de auteurs van recentere meta-analyses meer primaire studies includeerden en anderen *abstracts* van conferenties excludeerden. De conclusies van de meta-analyses variëren doordat heterogeniteit en *publication bias* verschillend werden geïnterpreteerd. De substantiële heterogeniteit en *publication bias* impliceren dat geïndividualiseerde plaatjesremmende therapie gebaseerd op genotype niet wordt ondersteund door de huidige beschikbare literatuur.

Hoofdstuk 21 beschouwt de enorme toename in het aantal meta-analyses binnen de cardiovasculaire geneeskunde. Deze trend leidt tot overlappende meta-analyses over hetzelfde onderwerp. Hoewel enige replicatie van onderzoek gewenst is, leidt een groot aantal overlappende (potentieel tegenstrijdige) meta-analyses tot inefficiëntie, verwarring en bedreiging van de wetenschappelijke waarde van de meta-analyse als studietype. Overlappende meta-analyses dienen te worden geëvalueerd aan de hand van overwegingen als heterogeniteit, *publication bias* en de kwaliteit van de individuele

primaire studies. Bovendien behoren auteurs de beweegredenen voor de (hernieuwde) meta-analyse te beschrijven, hun project te registreren in daartoe bestemde databases en dienen zij zich te houden aan de betreffende richtlijnen.

Hoofdstuk 22 is een brief aan de *editor* die het belang benadrukt van correcte methodologie in de vergelijking van de overleving van een specifieke patiëntenpopulatie (patiënten die SAVR ondergingen) versus de overleving van de algemene bevolking.

Hoofdstuk 23 is een brief aan de *editor* over de invloed van methodologie en aannames op de resultaten van kosteneffectiviteitsanalyses over TAVI. De methodologie voor het modelleren van utiliteiten, extrapoleren van *survival* en de aannames betreffende de *input* van het model beïnvloeden de uitkomsten van kosteneffectiviteitsanalyses.

Hoofdstuk 24 bediscussieert de generaliseerbaarheid en interpretatie van de resultaten van een *patient-level* meta-analyse die CABG en PCI vergelijkt tussen verschillende leeftijdscategorieën.

CHAPTER 28

List of Publications

1. **Osnabrugge RL**, Kappetein AP, Janssens AC. Carriage of reduced-function CYP2C19 allele among patients treated with clopidogrel. *JAMA.* 2011;305:467-468; author reply 468.
2. **Osnabrugge RL**, Head SJ, Kappetein AP. Methodologic issues regarding background mortality in observational studies. *J Thorac Cardiovasc Surg.* 2011;142:1289-1290; author reply 1290.
3. **Osnabrugge RL**, Head SJ, Kappetein AP. Transcatheter aortic valve implantation (TAVI): risky and costly, or challenging and promising? *BMJ.* Letter to the editor. 15 August 2012.
4. **Osnabrugge RL**, Head SJ, Genders TS, Van Mieghem NM, De Jaegere PP, van der Boon RM, Kerkvliet JM, Kalesan B, Bogers AJ, Kappetein AP, Hunink MG. Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. *Ann Thorac Surg.* 2012;94:1954-1960.
5. **Osnabrugge RL**, Head SJ, Bogers AJ, Kappetein AP. Towards excellence in revascularization for left main coronary artery disease. *Curr Opin Cardiol.* 2012;27:604-610.
6. **Osnabrugge RL**, Head SJ, Bogers AJ, Kappetein AP. Patient selection for transcatheter aortic valve replacement: what does the future hold? *Expert Rev Cardiovasc Ther.* 2012;10:679-681.
7. **Osnabrugge RL**, Head SJ, Bogers AJ, Kappetein AP. Appropriate coronary artery bypass grafting use in the percutaneous coronary intervention era: are we finally making progress? *Semin Thorac Cardiovasc Surg.* 2012;24:241-243.
8. **Osnabrugge RL**, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol.* 2013;62:1002-1012.
9. **Osnabrugge RL**, Speir AM, Head SJ, Fonner CE, Fonner E, Jr., Ailawadi G, Kappetein AP, Rich JB. Costs for surgical aortic valve replacement according to preoperative risk categories. *Ann Thorac Surg.* 2013;96:500-506.
10. **Osnabrugge RL**, Head SJ, Bogers AJ, Kappetein AP. Multivessel coronary artery disease: quantifying how recent trials should influence clinical practice. *Expert Rev Cardiovasc Ther.* 2013;11:903-918.
11. **Osnabrugge RL**, Kappetein AP. Impact of methodology and assumptions in a cost-effectiveness analysis on transcatheter aortic valve replacement. *J Thorac Cardiovasc Surg.* 2013;145:607.
12. **Osnabrugge RL**, Kappetein AP, Reynolds MR, Cohen DJ. Cost-effectiveness of transcatheter valvular interventions: economic challenges. *EuroIntervention.* 2013;9 Suppl:S48-54.

13. **Osnabrugge RL**, Capodanno D, Cummins P, Kappetein AP, Serruys PW. Review and recommendations on the current practice of meta-analyses: a guide to appraise the evidence. *EuroIntervention.* 2014;9:1013-1020.
14. **Osnabrugge RL**, Kappetein AP, Serruys PW. Non-cardiac surgery in patients with severe aortic stenosis: time to revise the guidelines? *Eur Heart J.* 2014;35:2346-2348.
15. **Osnabrugge RL**, Speir AM, Head SJ, Fonner CE, Fonner E, Kappetein AP, Rich JB. Performance of EuroSCORE II in a large US database: implications for transcatheter aortic valve implantation. *Eur J Cardiothorac Surg.* 2014;46:400-8.
16. **Osnabrugge RL**, Head SJ, Zijlstra F, Ten Berg JM, Hunink MG, Kappetein AP, Janssens AC. A systematic review and critical assessment of 11 discordant meta-analyses on reduced-function CYP2C19 genotype and risk of adverse clinical outcomes in clopidogrel users. *Genet Med.* 2014; In Press.
17. **Osnabrugge RL**, Speir AM, Head SJ, Jones PG, Ailawadi G, Fonner CE, Fonner E Jr, Kappetein AP, Rich JB. Prediction of costs and length of stay in coronary artery bypass grafting. *Ann Thorac Surg.* 2014;98:1286-93.
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19. **Osnabrugge RL**, Magnuson EA, Serruys PW, Campos CM, Wang K, Van Klaveren D, Farooq V, Abdallah MS, Li H, Vilain KA, Steyerberg EW, Morice MC, Dawkins KD, Mohr FW, Kappetein AP, Cohen DJ. A European perspective on the Cost-Effectiveness of Percutaneous Coronary Intervention with Drug-Eluting Stents vs. Bypass Surgery for Patients with Three-Vessel or Left Main Coronary Artery Disease: Final Results from the SYNTAX Trial and economic application of the SYNTAX Score II. Submitted.
20. **Osnabrugge RL**, Arnold SV, Reynolds MR, Magnuson EA, Wang K, Gaudiani V, Stoler R, Burton T, Kleiman N, Reardon MJ, Adams DH, Popma JJ, Cohen DJ. Health Status after Transcatheter Aortic Valve Replacement in Patients at Extreme Surgical Risk: Results from the CoreValve U.S. Trial. *JACC Cardiovasc Interv.* 2014; In Press.
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catheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. *J Am Coll Cardiol.* 2013;62:210-219.

24. Mylotte D, **Osnabrugge RL**, Martucci G, Lange R, Kappetein AP, Piazza N. Failing surgical bioprosthesis in aortic and mitral position. *EuroIntervention.* 2013;9 Suppl:S77-83.
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28. Kappetein AP, **Osnabrugge RL**. Commentary to "Survival Prediction Models for Coronary Intervention: Strategic Decision Support." *Ann Thorac Surg.* 2014;97:528-529.
29. Kappetein AP, **Osnabrugge RL**, Head SJ. Patient selection for TAVI in 2014: is there a justification for treating low- or intermediate-risk patients? The surgeon's view. *Eurointervention.* 2014;10 Suppl: U11-15.
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BOOK CHAPTER

Head SJ, **Osnabrugge RL**, Bogers AJ, Kappetein AP: "Management of stable coronary artery disease". Modena: FB Communication.

CHAPTER 29

PhD-Portfolio

Name PhD student:	Ruben Leendert Jan Osnabrugge
Erasmus MC department:	Cardio-Thoracic Surgery
Research School:	Cardiovascular Research School (COEUR), Erasmus MC
Promotor:	Prof.dr. A.P. Kappetein

ACADEMIC EDUCATION

2009-2012 MSc in Clinical Epidemiology, NIHES, Rotterdam, the Netherlands
2007-2011 Doctorate (MSc) in Medicine, Erasmus MC, Rotterdam, the Netherlands
2006-2007 Propaedeutic Dutch Law, Law College University of Utrecht, the Netherlands
2006-2008 Honoursclass Erasmus School of Economics, Erasmus University Rotterdam, the Netherlands
2005-2008 BSc in Economics, minor Health Economics, Erasmus University Rotterdam, the Netherlands

PHD TRAINING

	Year	ECTS
Oral presentations (9.0)		
COEUR seminar on percutaneous valves (Rotterdam)	2012	0.6
Dutch Association for Cardio-Thoracic Surgery (Utrecht)	2012	0.6
EuroPCR (Paris, France)	2012	0.6
Transcatheter Cardiovascular Therapeutics (Miami FL, USA)	2012	0.6
European Association of Cardio-Thoracic Surgery (Barcelona, Spain)	2012	1.2
Dutch Association for Cardio-Thoracic Surgery (Utrecht)	2012	0.6
Society of Thoracic Surgeons (Los Angeles CA, USA)	2013	0.6
Dutch Association for Cardio-Thoracic Surgery (Utrecht)	2013	0.6
European Association of Cardio-Thoracic Surgery (Vienna, Austria)	2013	1.2
Virginia Cardiac Surgery Quality Initiative (Charlottesville VA, USA)	2013	1.2
BRS-ARC meeting (Rotterdam)	2014	0.6
Dutch Association for Cardio-Thoracic Surgery (Utrecht)	2014	0.6
Poster presentations (1.2)		
EuroPCR (Paris, France)	2013	0.6
Transcatheter Cardiovascular Therapeutics (San Francisco CA, USA)	2013	0.6
Conferences (12.3)		
European Association of Cardio-Thoracic Surgery (Lisbon, Portugal)	2011	1.2
EuroPCR (Paris, France)	2012	1.2
Transcatheter Cardiovascular Therapeutics (Miami FL, USA)	2012	1.2

	Year	ECTS
European Association of Cardio-Thoracic Surgery (Barcelona, Spain)	2012	1.2
Society of Thoracic Surgeons (Los Angeles CA, USA)	2013	1.2
EuroPCR (Paris, France)	2013	1.2
European Association of Cardio-Thoracic Surgery (Vienna, Austria)	2013	1.2
Transcatheter Cardiovascular Therapeutics (San Francisco CA, USA)	2013	1.2
Dutch Association for Cardio-Thoracic Surgery (Utrecht)	2011-2014	1.5
European Association of Cardio-Thoracic Surgery (Milan, Italy)	2014	1.2
In-depth courses (6.1)		
Decision analysis in Clinical Research, Harvard School of Public Health (Boston MA, USA)	2011	2.1
Health Services Research, Harvard School of Public Health (Boston MA, USA)	2011	2.1
Chronic Diseases (Cardiovascular), University of Cambridge (Cambridge, UK)	2012	1.1
Good Clinical Practice Training (Rotterdam)	2012	0.8
Courses, seminars and meetings (6.2)		
Coeur PhD day (Rotterdam)	2012	0.3
American College of Cardiology Gender Data Forum (Washington DC, USA)	2012	0.3
Virginia Cardiac Surgery Quality Initiative meeting (Fairfax VA, USA)	2012	0.3
Mitral Valve Academic Research Consortium meeting (Washington DC, USA)	2012	0.3
Local scientific meetings of Dept. of Cardio-Thoracic Surgery (Rotterdam)	2010-2014	3.0
Local scientific meetings of Mid America Heart Institute (Kansas City MO, USA)	2013-2014	2.0
Teaching (2.6)		
Supervising students and clinical researchers	2012-2014	2.0
Workshops on PhD training at Career day at the Erasmus University Medical School	2014	0.6
Academic positions (4.0)		
Editor Journal and News Scan, The Cardio-Thoracic Surgery Network (CTSNet)	2013-present	2.0
Associate editor Eurointervention (Rotterdam)	2013-present	2.0
Peer reviewer international scientific journals (3.3)		
The Annals of Thoracic Surgery	2012-present	1.0
Circulation	2014-present	0.5
European Heart Journal	2013-present	0.5
Eurointervention	2013-present	0.5
European Journal of Cardio-Thoracic Surgery	2013-present	0.5
Medical Decision-Making	2013-present	0.3

CHAPTER 30

Dankwoord
Acknowledgements

"Silent gratitude isn't very much use to anyone."

Gertrude Stein

...and so, finally, it's time to thank those who have been involved and supportive of this thesis!

First and foremost, there is one major person whom I cannot thank sufficiently enough: my promotor Prof.dr. A.P. Kappetein.

Dear Pieter,
It's amazing what a *Marktplaats* bike advert can bring about.
I am very fortunate to have you as my mentor! You gave me trust and countless opportunities. Your personal guidance made me grow as a clinical researcher and as a person; you truly know how to bring out the best in people. Thank you for opening up your international network which allowed me to make my PhD an even more memorable experience.

I admire your passion, energy, work ethic, social skills and '*levenskunst*.' It is extraordinary how you manage to combine so many different activities successfully, in order to push the boundaries in cardiovascular medicine. You seem insensitive to fatigue and always find ways to combine *business* (discussing papers, work meetings) with pleasure (dinner, green egg, wine, and good coffee). I respect the way you are genuinely interested in a pupil's view.

Moreover, I now know how to find the best flights within seconds and how to select the right line at immigration at Heathrow or LAX. I hope to continue to learn from you and pass on your vision to others. Thank you!

Prof.dr. Bogers, dank u voor het vertrouwen om mij als promovendus aan te stellen. U schiep de juiste voorwaarden voor deze thesis, was altijd bereid tot meedenken en ondersteuning bij het opzetten van nieuwe projecten en samenwerkingen. Uw gebalanceerde uitstraling van rust, vertrouwen en weloverwogenheid zijn een voorbeeld voor me.

De vooruitgang in cardiovasculaire interventies is ontegenzeggelijk een team prestatie van hartchirurgen en (interventie)cardiologen. Het was voor mij een eer om te mogen samenwerken met vooraanstaande cardiologen van het wereldberoemde Thoraxcentrum in Rotterdam. Prof.dr. De Jaegere: uw betrokkenheid en vriendelijkheid zorgden ervoor dat ik mij welkom voelde om met u en uw groep samen te werken.

Prof.dr. Serruys, a driving force behind the world fame of the Thoraxcenter. You are an important reason why doors opened whenever I mentioned that I was a PhD fellow

from Rotterdam. I appreciated our discussions on the usefulness of cost-effectiveness analyses. Thank you for the collaboration and the opportunities you gave me within Cardialysis and EuroIntervention.

Nicolas Van Mieghem, dank voor de plezante samenwerking en hulp. Jouw combinatie van doelgerichtheid, (sociale) intelligentie en humor maken het verschil. Ik zal nog vaak naar je sportprestaties vragen.

Prof.dr. Zijlstra, dank voor het leiden van de afdeling cardiologie en uw input voor de paper over *CYP2C19* en clopidogrel response.

I am very thankful to Prof.dr. Cohen.
Dear David, when we met at EACTS 2012, you recognized my interest in cost-effectiveness analyses. You immediately invited me to visit the Health Economics & Technology Assessment (HETA) Research Group at the Mid-America Heart Institute (MAHI) in Kansas City. During the nine months that I spent in the Mid-West, you created the perfect conditions for me to immerse in the world of cost-effectiveness and quality-of-life studies. Thank you so much for this opportunity to learn from the best. Your research group is perfectly tuned and you made sure that I was able to learn from the analyses, the processes in your research group, as well as the medical writing process. The SYNTAX analyses form the core of my thesis and I owe them to you. Also, I admire your work ethic; you seem to constantly think of solutions to statistical challenges and I cannot think of any time during the day at which I wouldn't get an email reply within 15 minutes. I feel privileged having you as my mentor and I am honored to have you in my doctoral committee.

Prof.dr. Elizabeth Magnuson, the statistical mastermind of the HETA group.
Dear Elizabeth, you made me feel welcome from the moment I stepped into your office. Your profound knowledge, combined with your social and managerial skills make the HETA group run smoothly. I really valued your efforts to fully involve me in the whole process of analyzing data. Your remarks on my progress were motivating and the occasional funny notes were greatly appreciated. Thank you!

Prof.dr. Hunink, Dear Myriam, thank you for supervising my first steps in science. Your courses on medical decision-making and cost-effectiveness analyses are world class and formed the foundation for this thesis. I admire your analytical skills and appreciated being part of your research group, in which quality, integrity and respect are key values. It is an honor to have you in my doctoral committee.

Prof.dr. Cecile Janssens, Dear Cecile, our interest in a paper on *CYP2C19* alleles and clopidogrel response took a course of its own. It was instrumental in teaching me how to

critically appraise research and write about science. I appreciate your quick-witted and open personality. Thank you for staying in touch after moving to Emory, and for crossing the Atlantic to be an opponent in my doctoral committee.

Prof.dr. Klautz en Prof.dr. Steyerberg, bedankt voor uw bereidheid om in mijn kleine commissie plaats te nemen en de wetenschap in dit proefschrift te beoordelen. Prof.dr. Kromhout, het is speciaal om u als opponent in mijn commissie te hebben. Dank voor uw spontane toezegging!

I am thankful to the Virginia Cardiac Surgery Quality Initiative (VCSQI) and its leadership including Jeffrey Rich, Alan Speir, and Gorav Ailawadi. You had the open-mindedness to collaborate with a group from Rotterdam and give me opportunities to do exciting research on the costs and quality of various cardiac surgical procedures. By inviting me to speak in Charlottesville, I experienced how quality improvement is done in practice. You made me part of your extraordinary collaborative group that aims to reduce costs by improving quality. Your vision and leadership are an inspiration and I am looking forward to continuous collaboration.

Dank aan de Rotterdamse thoraxchirurgen en (oud) arts-assistenten voor de getoonde interesse in mijn onderzoek en de goede sfeer op de kamer en afdeling. Ik hoop nog veel klinische en operatieve vaardigheden van jullie te mogen leren.

Veel dank aan de onderzoekscoördinatoren, datamanagers, en medewerkers van het secretariaat thoraxchirurgie. Annet dank voor je betrokkenheid en Els, dank voor je hulp bij database verzoeken, zelfs op afstand toen ik de Verenigde Staten was.

Beste Rianne, dank voor je ondersteuning van allerhande activiteiten op de afdeling en voor EACTS. Je nuchtere kijk is verfrissend en de gezelligheid die je meebrengt, mag niet worden onderschat.

Maaike ,Richard, Jeanette, Sjaak, Dwight, Jasper Haverkamp en Anne-Marie Maugenest, dank voor jullie interesse in mijn onderzoek en hulp bij de kosten-onderzoeken op de OK en Cathlab.

A big thank you to the staff at Cardialysis and Eurointervention: Gerrit-Anne van Es, Paul, Sylvie, Wendel and Hanny. Thank you for thinking of me, giving me opportunities and making me feel welcome.

The dream team from Windsor: Kathy, Amanda, Sharon, Elvira, Diana, and Elka. Thank you for your help before, during, and after the Annual Meetings.

One of the aspects I have greatly enjoyed is the international collaboration with fellow researchers around the globe. I have had the privilege to work with established international leaders including Friedhelm Beyersdorf, Volkmar Falk, Teresa Kieser, Sir Bruce

Keogh, Rüdiger Lange, Nicolo Piazza, Duane Pinto, Michael Mack, Douglas Mathisen, Neil Moat, Marie Claude Morice, Friedrich Mohr, Thomas Modine, Vuyisile Nkomo, Domenico Pagano, John Pepper, Matthew Reynolds, Rafael Sadaba, Miguel Sousa d'Uva, and Douglas Wood. Thank you very much for maintaining a fruitful international scientific environment and for allowing me to get involved. A special thanks to Joel Dunning, who introduced me to CTSNet and is an amazing and reliable TV host in the EACTS TV studio sessions.

Moreover, thanks to all my co-authors and young, ambitious international colleagues. Darren Mylotte, Chris Meduri, Davide Capodanno, Heng Zhang, and Andreas Rück: it has been a pleasure to work with the future of cardiovascular medicine and I wish you the best of luck with your projects and careers. I am looking forward to work with you again.

The group at the Mid-America Heart Institute showed me how research is done in the Mid-West: a friendly and warm professional way of collaborating. A special thank you to the research leaders John Spertus, Carole Decker, Mikhail Kosiborod, Paul Chan, and Suzanne Arnold. Collaborating with and learning from you has been a joy. A major thank you to the statistical powerhouse (Phil Jones, Kate, Kaijun, Khaja, and Haiyan), thanks to my roomies Federico, Kevin, John, Sandy, and thank you Donna for looking after me.

The fellows Natalie, Mouin, Faraz, Tim, Anna, Praneed, and Jason took care of the good vibe and made me feel welcome instantly. I know you guys still think Sinterklaas is a rip-off Santa Claus, but actually it's the other way around. Please do your homework.

Natalie, I really appreciated your efforts to take care of me and being creative in making up reasons why I should stay in Kansas City and become a U.S. citizen. Thanks also to your husband JT, who is obsessed with Dutch words. Here's to you JT: Dank je wel! Little Fiona is blessed to have you as her parents. Mouin and Patricia, thanks for the friendship and wearing orange on the Dutch Kings Day and during the World Cup! Faraz, thanks for introducing me to Mountain Dew and later on for saving my life by making me aware of its caffeine content. The Sporting KC game, BBQ-lunches and farewell dinners are special memories. Thanks guys!

My stay in the US was filled with authentic American hospitality. This thesis wouldn't have been the same without the support of the late Ed Fonner. It was overwhelming how Ed wanted to help me with my career as well as with my stay in Kansas City. He connected me with the right people and made sure I drove a '89 Chevy Silverado. He was the soul of VCSQI and I wish he could have been witness to the finalization of my PhD. His son Eddie is doing a terrific job as the new driving force behind VCSQI and I know few people that have a warmer heart than Maribeth. Thank you Fonner family!

Bill and Uta, thanksgiving dinner with you and your family was memorable. You showed me Dallas and how a good team can combine a busy CT-surgeon's job with the true spirit

of family life. Feel welcome when you make a trip to the Netherlands. Heather and Jan, thanks for your interest and showing me Chicago.

The ART Group guided me in my first scientific project: thank you Tessa, Bart, Bob, Nathalie, Farzin, Suman, Raluca, John, and Erica! Colleague PhD researchers at the Thoraxcenter: Aart, Bardia, Carina, Catalina, Elrozy, Gerdien, Jonathan, Milan, Nelleke, Robert, Rutger-Jan en Sahar, thank you for the good atmosphere and I wish you the best of luck with your careers!

Beste Stuart, de meeste tijd van mijn promotie heb ik met jou doorgebracht. De mix van *business and pleasure* was bijzonder. Ik heb veel van je geleerd, veel met je gediscussieerd en heel veel met je gelachen. Dank voor een fantastische tijd. Met je analytische denkwijze, doelgerichtheid en doorzettingsvermogen ga je een mooie carrière tegemoet. Veel succes!

Mostafa, jouw wijsheid en CV lijken niet overeen te komen met je leeftijd. Ik vind het prettig om met je samen te werken en wens je veel succes met het verwezenlijken van je dromen.

Dit promotietraject was niet alleen een beroepsmatig, maar ook een persoonlijk avontuur. Ik wil al mijn vrienden en familie bedanken. Ik heb het geluk dat ik me altijd gesteund heb gevoeld door dierbaren die mij een warm hart toe dragen. Dit dankwoord is niet compleet zonder hen.

Clasine, Christine en Martijn: jullie betrokkenheid is groot. Geen Huskbus kan onze vriendschap aantasten en het is bijzonder hoe we de hele wereld overvliegen om samen avonturen te ondernemen!

Maren: jij wist precies de goede steun te geven toen dat nodig was, veel dank. Je nuchtere blik is heerlijk en ik kijk nu al uit naar jouw verdediging!

Marijn: dank voor je wijze raad, Top Gear, goede wijn, fietsen, en humor. They go a long way in writing a PhD thesis.

Inger-Elze, Marnix, Joost, Niels, Jef, Maurits, Stefan en Jan-Willem, Jonghe 8 2009: dank voor het begrip teamwork! Jullie kunnen veel meer dan alleen hard roeien. Het verwisselen van (veel) samen ergometeren voor (veel) samen eten, bevalt me overigens uitstekend.

Irene Fleur en Niek, leuk dat we elkaar zovele jaren na het JvO nog zien. Het stimuleert me om jullie verhalen te horen en ik ben benieuwd naar jullie 'boekjes'. Gerald, dank voor onze langdurige vriendschap. Matthieu, jij gaf me het laatste zetje om toch vooral voor die promotieplek te gaan. Veel dank daarvoor, net zoals voor je gezelligheid, relativeringsvermogen en scherpzinnigheid.

Beste Stefan, ik prijs me gelukkig met een vriend als jij. Jij hebt aan één oogopslag voldoende om me te begrijpen, of het nu gaat om life-events of een mooie grap. Dank voor je support, ongekende betrokkenheid, en voor het feit dat jij mijn paranimf wilt zijn.

Martijn, jij bent de belangrijkste reden dat ik blij ben ooit met Economie & Rechten te zijn begonnen. Ik waardeer het hoe je altijd doorvraagt; mede daardoor is onze vriendschap altijd blijven groeien. Het is geen toeval dat jij mijn paranimf bent.

Marije, lieve zus, ik ben vast niet altijd het ideale broertje geweest, maar ik denk dat we er aardig uit zijn gekomen. Ik bewonder jouw idealisme, en hoe jij je eigen weg durft te gaan. Straks zijn wij allebei gepromoveerd. Voor jou geen PubMed, patiëntendata en SPSS, maar écht speurwerk. Het leek mij sisyfusarbied en ik heb veel respect voor de volharding die je hebt getoond. De archieven van Napels kennen voor jou nu geen geheimen meer en ik kijk uit naar je verdediging. Ik ben supertrots op jou!

Oma, mijn voorbeeld voor wilskracht. Uw betrokkenheid doet me veel en ik ben dankbaar dat ik nog zoveel met u kan delen. Veel liefs!

Lieve papa en mama, de onvoorwaardelijke warmte en liefde die jullie me geven zijn onbeschrijfelijk. Jullie weten me op een prettige manier te stimuleren en af te remmen als ik weer eens té snel té veel wil. Ik ben me steeds bewuster van de solide basis die jullie mij gaven. Het heeft ervoor gezorgd dat ik blij mezelf kan zijn. Dit proefschrift is voor jullie.

Lieve Marijke, *you blew me away*! Onze eerste teamprestatie zit er bijna op. Jouw liefde, enthousiasme en steun zijn overweldigend. Ik geniet ervan hoe jij sprankelt en heb veel zin in onze nieuwe avonturen.

"Let us be grateful to people who make us happy; they are the charming gardeners who make our souls blossom."

Marcel Proust

CHAPTER 31

About the Author

Ruben Leendert Jan Osnabrugge was born on October 7, 1986, in Soest, the Netherlands. He attended the Johan van Oldenbarnevelt Gymnasium in Amersfoort, from which he graduated in 2005.

In the same year he started his studies in Economics & Business at Erasmus University Rotterdam. In addition, he obtained a propaedeutic exam in Dutch Law from Utrecht Law College in 2007 and simultaneously started medical school at Erasmus University in Rotterdam. In 2008, alongside his medical studies, he completed his Bachelor's program in Health Economics and its accompanying Honours Class. In 2009, Ruben was selected to participate in a special program for medical students, offered by the Netherlands Institute of Health Sciences (NIHES). This program enabled him to combine a Master of Science in Clinical Epidemiology with his Medical Degree. The Master's program consisted of summer and winter schools during recess periods. Part of this program was spent at the Harvard School of Public Health, Harvard University, Boston, MA, U.S.A., and the Cambridge Institute of Public Health, Cambridge University, U.K. For his research project, Ruben worked at the departments of Epidemiology and Cardio-Thoracic Surgery under the supervision of Prof.dr. Myriam Hunink and Prof.dr. A. Pieter Kappetein. This resulted in his first publication. Furthermore, Ruben was student chairman of the Steering Committee of his medical school (2008-2010) and representing member in the University Council (2010-2011).

After obtaining his M.Sc. degrees in Medicine (2011) and Clinical Epidemiology (2012), he started his Ph.D. research at the department of Cardio-Thoracic Surgery, under the supervision of Prof.dr. A. Pieter Kappetein. His work focuses on the costs, quality and value of cardiovascular interventions.

In 2013, Ruben received a Fulbright Scholarship from the Dutch Minister of Education. This allowed him to spend part of his Ph.D. research in the United States. Between February 2013 and January 2014 he worked as research fellow for the Health Economics and Technology Assessment group of the Mid-America Heart Institute, Kansas City, MO, U.S.A. This group has a longstanding interest in cardiovascular outcomes research and in particular in using data from clinical trials and registries to help improve medical decision-making and health care policy. Under the direct supervision of Dr. David Cohen and Dr. Elizabeth Magnuson, he acquired additional knowledge and experience in the fields of quality of life studies and cost-effectiveness analyses.

Ruben collaborates with the Virgina Cardiac Surgery Quality Initiative (VCSQI), a voluntary consortium covering 99% of all cardiac surgical centers in the Commonwealth of Virginia, U.S.A. Learning from its leadership, including Dr. Alan Speir, Dr. Gorav Ailawadi and Dr. Jeffrey Rich, Ruben investigates the opportunities for reducing costs by improving quality.

In October 2013, Ruben was awarded the European Association of Cardio-Thoracic Surgery (EACTS) Young Investigator Award for the best manuscript in the cardiac domain. Moreover, he is associate editor of the journal *EuroIntervention*, member of the research and writing committee of the VCSQI, and editor of the *Journal and News Scan of the Cardio-Thoracic Surgery Network* (CTSNet), which regularly sends out e-mail blasts to 40,000 cardio-thoracic surgeons around the world.

Currently, Ruben is doing his clinical rotations at various hospitals in the Rotterdam area, which he expects to complete in early 2016.

Financial support for the publication of this thesis was generously provided by:

ARMUS Corporation
Cardialysis
www.ee-group.com
Erasmus Universiteit
Krijnen Medical Innovations
St Jude Medical Netherlands
MAQUET Netherlands
QP&S
Sorin Group
Takeda
Thoraxcentrum Research BV
Vascutek Nederland

isbn: 978-94-6169-612-0