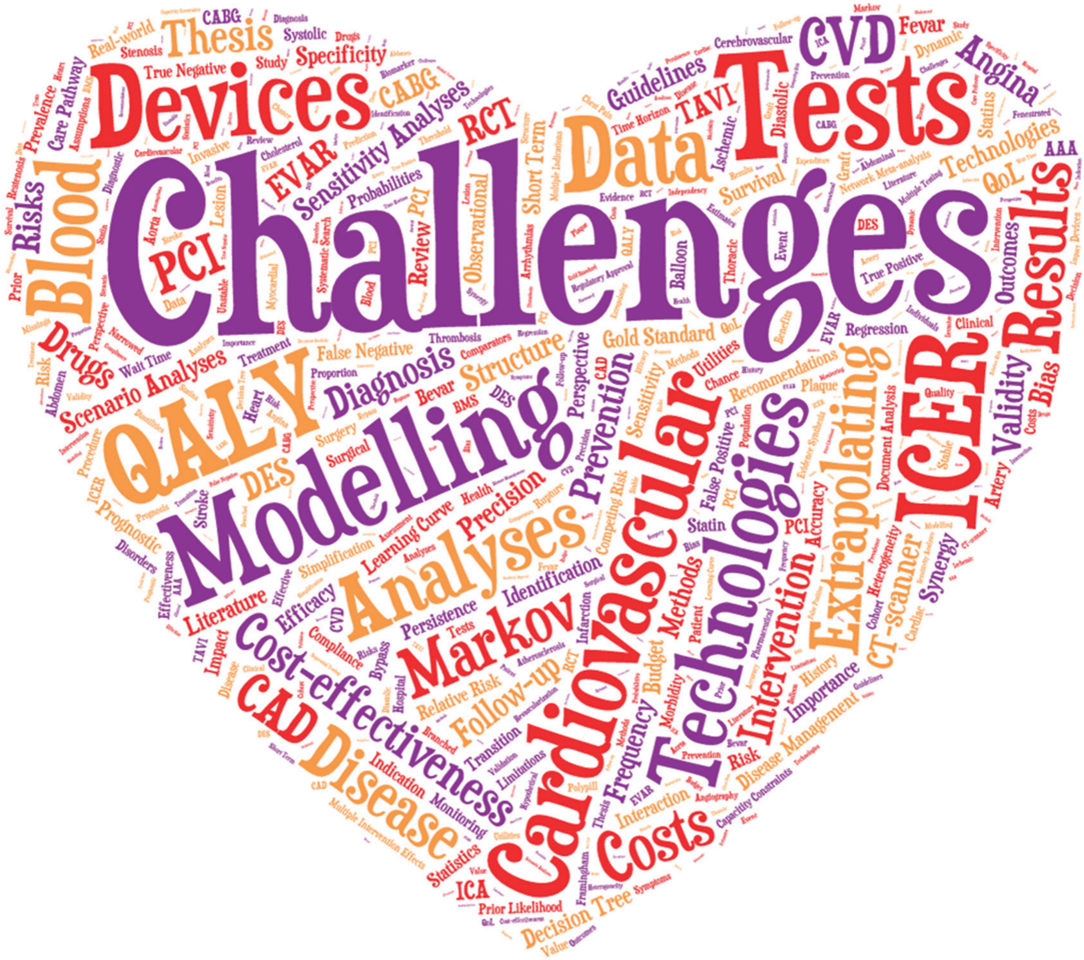

Challenges in assessing the cost-effectiveness of cardiovascular disease technologies

Laura Burgers

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Uitdagingen in het berekenen van de kosten-effectiviteit van hart-en vaatziekte technologieën

Laura Theodora Burgers

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Uitdagingen in het berekenen van de kosten-effectiviteit van hart-en vaatziekte technologieën

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Contents

Abbreviations

AAA	abdominal aorta aneurysm
ASA	American Society of Anaesthesiology
bEVAR	branched endovascular aneurysm repair
BMI	body mass index
BMS	bare-metal stent
CABG	coronary artery bypass graft
CAD	coronary artery disease
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CT	computed tomography
CTCA	computed tomography coronary angiography
CUA	cost-utility analysis
CVA	cerebrovascular accident
CVD	cardiovascular disease
DBP	diastolic blood pressure
DES	drug-eluting stent
DESM	discrete event simulation
DMP	disease management programme
DPM	disease progression model
DT	decision tree
DVT	deep venous thrombosis
EQ-5D	EuroQol 5D
ESC	European Society of Cardiology
EVAR	endovascular aneurysm repair
fEVAR	fenestrated endovascular aneurysm repair
FN	false negative
FP	false positive
FRS	Framingham risk score
HPM	healthy person model
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
ICA	invasive coronary angiography
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
JRAAA	juxta-renal abdominal aortic aneurysm
LT	life time
MCS	mental component scores
MI	myocardial infarction
NA	not applicable
NGCCT	new generation dual-source coronary computed tomography
NIHR	National Institute for Health Research
NSTEMI	non-ST elevation myocardial infarction
NYHA	New York heart association class
OSR	open surgical repair
PCI	percutaneous coronary intervention
PCS	physical component scores
PE	pulmonary embolism
PES	paclitaxel-eluting stent
PSA	probabilistic sensitivity analysis
PTCA	percutaneous transluminal coronary angioplasty
PVD	peripheral vessel disease
QALY	quality adjusted life years
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
SBP	systolic blood pressure
SCORE	systematic coronary risk evaluation
SD	standard deviation
SE	sensitivity
SES	sirolimus-eluting stent
SF-36	short form
SP	specificity
STM	state-transition model
TAAA	thoraco-abdominal aortic aneurysm
TIA	transient ischaemic attack
TIMI	thrombolysis in myocardial infarction
TLR	target lesion revascularization
TN	true negative
TP	true positive
TVR	target vessel revascularization
WTP	willingness-to-pay
YRM	York radiation model
ZES	zotarolimus-eluting stent


Challenges
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Chapter 1

Introduction and Outline

Despite improvement in the prognosis of patients with cardiovascular disease (CVD) it still remains the second leading cause of death across the Western world[1]. In the Netherlands in 2013, approximately 39,000 people died of CVD and it is the second leading cause of death after cancer[1]. However, CVD still is the leading cause of death for females, particularly in the older age categories[1]. Besides mortality, CVD also has a major impact on morbidity; in the Netherlands more than 1 million persons have CVD[2]. Furthermore, in 2010 282,000 patients were admitted to the hospital due to CVD[3]. The total hospital admission frequency in the Netherlands in 2010 was 1,366 per 10,000 individuals, CVD resulted in a hospital admission frequency of 170 per 10,000 individuals[4]. Furthermore, patients with CVD have a reduced quality of life (e.g. angina pectoris -0.0412) compared with the general population[5,6].

Cardiovascular disease

Cardiovascular disease is an umbrella term for many different diseases, including coronary artery disease (CAD) (e.g. angina pectoris), vascular diseases [e.g. abdominal aorta aneurysm (AAA)], arrhythmias (e.g. atrioventricular block), congenital heart diseases (e.g. ventricular septal defect) and cerebrovascular diseases (e.g. transient ischaemic attack). Some diseases are present at birth whereas others are the result of atherosclerosis which is a slow but progressive pathological process that leads to narrowing and hardening of the arteries. The risk of experiencing a cardiovascular event (e.g. myocardial infarction or stroke) increases with various factors, including age, systolic blood pressure and total cholesterol. Furthermore, men and smokers have a higher risk of a cardiovascular event than women and non-smokers[7]. In addition, psychosocial factors seems to contribute to the pathogenesis of CVD[8]. For primary prevention of CVD, the SCORE risk function[7] or the Framingham risk equation[9] is often used to determine the 10-year risk of developing a cardiovascular event. Based on the results of the risk functions the type of treatment (e.g. statins) is determined.

Most of the treatments for CVD are focused on preventing primary and secondary events due to CAD which accounts for the largest proportion (25%) of CVD deaths in the Netherlands[1]. Many treatment options for CAD involves non-pharmaceutical technologies (e.g. coronary stents), which are also often used for patients with other CVD disorders such as aortic aneurysms that accounts only for 2% of the CVD deaths[1]. The research area of this thesis is on CVD with a main focus on CAD and aortic aneurysms.

Coronary artery disease

Patients can be diagnosed with CAD if the coronary arteries are affected by atherosclerosis. Atherosclerosis reduces blood flow in the coronary arteries in such a way that the oxygen demands cannot be fulfilled and this can lead to chest pain (i.e. angina). Angina can be classified into stable or unstable angina, depending on the degree of clinical symptoms. Patients with stable angina have angina symptoms (e.g. chest pain) only with exertion or stress. In contrast,

patients with unstable angina have angina symptoms that occur without exertion and do not stop with rest. Besides narrowing, a lesion could also be obstructed due to a ruptured plaque leading to an event like myocardial infarction (MI) or a cardiac arrest.

When patients are suspected of CAD due to clinical symptoms, a computed tomography (CT) angiography or an invasive coronary angiography (ICA) is often performed to determine the degree of narrowing (stenosis) in the arteries. Patients with ≥70% diameter narrowing of at least one major epicardial artery segment or ≥50% diameter stenosis in the left main coronary artery[10] are considered to have significant CAD and are often offered medication in combination with a revascularization procedure (i.e., percutaneous coronary intervention (PCI) or a coronary artery bypass graft (CABG)) to restore oxygen supply. These treatments, often based on the results of a diagnostic test, aim at relieving symptoms, preventing progression and plaque rupture. A PCI is an endovascular treatment that restores blood flow by reopening the lesion and consequently symptoms are relieved. Originally, angioplasty was performed with an expanding balloon to dilate the narrowed segment of the artery but this has been combined with a bare-metal stent (BMS) since 1994 to ensure that the segment remains dilated. Compared with balloon angioplasty, BMS reduces restenosis (reoccurrence of stenosis) which often requires a repeat revascularization[11]. Since the frequency of restenosis was still substantial after BMS, drug-eluting stents (DES) were developed and came to market in 2003 to reduce the frequency of restenosis even more. However, some studies suggest that patients treated with DES may have a higher chance of developing very late stent thrombosis[12]. CABG is a more invasive intervention than PCI since the chest cavities need to be opened and the heart often needs to be stopped ('on-pump' bypass). A CABG restores the blood flow by diverting the flow of blood around a section of a blocked artery using an artery from another part of the body.

Aneurysms of the aorta

An aneurysm of the aorta is defined as a widening that is more than 50% of the normal diameter of the vessel, partially caused by atherosclerosis. Seventy-five percent of the aneurysms involving the aorta are located in the abdomen [abdominal aortic aneurysm (AAA)], below the diaphragm, and usually located below the renal arteries. Patients with an AAA are often asymptomatic and a sonography or CT scan is required to diagnose patients with AAA. Depending on the age group studied and the definition of AAAs, screening studies have shown that 1.3–12.7% of the population have an AAA[13]. Nowadays, patients with an AAA diameter larger than 5.5 cm are treated with an open surgical repair (OSR) or endovascular aneurysm repair (EVAR) to prevent rupture. Most patients can be treated with EVAR depending on the access of the iliac artery (e.g. diameter or tortuosity), and the angulation, diameter and length of the neck. In an OSR, the abdominal cavity need to be opened to repair the aneurysm with a graft. EVAR is a less invasive technique where a stent graft is inserted through the common femoral artery. When the aneurysm is located close to the origin of the renal arteries (juxta-renal abdominal aortic aneurysm) or in both the thoracic

and abdomen (thoracoabdominal aortic aneurysms) and patients are not fit for surgery, EVAR might not be possible. Fenestrated (fEVAR) and branched EVAR (bEVAR) can be considered for these patients, respectively. FEVAR/bEVAR are more complex procedures than EVAR due to the branches and fenestrations allowing blood flow to the organs.

Cost-effectiveness of cardiovascular interventions

In 2012, health care expenditure as a percentage of gross domestic product was approximately 17.9% in the US, 12.4% in the Netherlands and 9.4% in the UK[14]. In the Netherlands, 9.2% of the total health care expenditure (approximately 8.3 billion euro) is spent on CVD[2]. Health care expenditures are rising globally due to aging populations and the development of new medical technologies[15]. Therefore, it is important to make wise choices when allocating the limited health care resources. Cost-effectiveness analyses can help in deciding between interventions for specific indications but also for interventions across indications.

Many non-pharmaceutical technologies (e.g. stents, prostheses and diagnostic tests) are used in the prevention, diagnosis, prognosis, monitoring, and treatment of CVD. Over the past few years, many new or improved non-pharmaceutical technologies for CVD have entered the market and it is therefore important to ascertain if these technologies are cost-effective compared with existing interventions.

AIM AND OUTLINE OF THIS THESIS

The overall aim of the thesis is to assess the cost-effectiveness of various technologies in CVD and to identify and deal with challenges in assessing the cost-effectiveness of CVD technologies.

Several studies are presented to demonstrate the assessment of the cost-effectiveness of technologies in CVD. First, the cost-effectiveness of a hypothetical test for primary prevention of CVD was estimated. Furthermore, various non-pharmaceutical technologies[†] are used as case studies for the assessment of the cost-effectiveness in the diagnosis and treatment of CAD and AAA. In addition, to these cost-effectiveness studies, analyses of treatment variation and health related quality of life of patients diagnosed with CAD are performed. Finally, we described the challenges that arise in modelling the cost-effectiveness of cardiovascular interventions in a review paper.

In **Chapter 2,** we study the potential cost-effectiveness, using modelling techniques, of a biomarker test that could be used to decide which individuals with an intermediate CVD risk would benefit from statin treatment. The cost-effectiveness of new generation coronary CT scanners versus ICA for difficult to image patients suspected of CAD or with CAD was estimated in **Chapter 3**. For that study, a literature based Markov model was developed to estimate the cost-effectiveness from an UK NHS perspective. Patients with CAD undergoing a PCI are often treated with BMS or DES stents and it is sometimes unclear what determined the choice of stent. We therefore explore in **Chapter 4** which factors lead to variation in stent choice in Dutch patients with stable or unstable CAD undergoing a PCI. **Chapter 5** describes which patient characteristics are associated with health related quality of life in Dutch patients with stable or unstable CAD undergoing a coronary angiography. In **Chapter 6**, we systematically summarized the available evidence on the cost-effectiveness of DES compared with BMS. In addition, we explored the added value of meta-regression analyses compared with conventional review methods to examine the variation in incremental costs and incremental effectiveness in terms of quality adjusted life years and repeat revascularizations avoided between studies. Patients with an AAA larger than 5.5.cm are often offered elective reparative treatment. In **Chapter 7,** we have estimated the cost-effectiveness of an endovascular approach compared with open surgical repair for a Dutch setting. In **Chapter 8,** we describe how the cost-effectiveness of fenestrated and branched endovascular aneurysm repair for juxta-renal and thoraco-abdominal aneurysms should be modelled when an UK NHS perspective is adopted. **Chapter 9** provides a thorough overview of challenges that currently exist in modelling the cost-effectiveness of various interventions for cardiovascular disease. Finally, in **Chapter 10**, the results of the studies are summarized and discussed; furthermore we recommend further research challenges.

[†] Throughout the thesis, non-pharmaceuticals we defined as medical devices and tests. With the exception of Chapter 9, we did not combine the two types of interventions and defined them as non-drug interventions (devices) and test interventions.


Challenges
Modelling
Cardiovascular
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Analyses
Extrapolating
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Markov
Cost-effectiveness
Disease
Costs
CAD
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Diagnosis
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Angina
Thesis
Specificity
Sensitivity
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RCT
Drugs
Scenario Analyses
Guidelines
TAVI
Precision
Follow-up
Prevention
Structure
Validity
Bias
Risks
Decision Tree
Gold Standard
False Negative
True Negative

Chapter 2

Is it cost-effective to use a test to decide which individuals with an intermediate cardiovascular disease risk would benefit from statin treatment?

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ABSTRACT

Background: The 2012 European guidelines recommend statins for intermediate-risk individuals with elevated cholesterol levels. Improved discrimination of intermediate-risk individuals is needed to prevent both cardiovascular disease (CVD) and statin side-effects (e.g. myopathy) efficiently since only 3–15 in every 100 individuals actually experience a cardiovascular event in the next 10 years. We estimated the potential cost-effectiveness of a hypothetical test which helps to determine which individuals will benefit from statins.

Methods and results: Prognosis of different age- and gender-specific cohorts with an intermediate risk was simulated with a Markov model to estimate the potential costs and quality-adjusted life-years for four strategies: treat all with statins, treat none with statins, treat according to the European guidelines, or use a test to select individuals for statin treatment. The test-first strategy dominated the other strategies if the hypothetical test was 100% accurate and cost no more than €237. This strategy and the treat-all strategy were equally effective but the test generated lower costs by reducing statin usage and side-effects. The treat-none strategy was the least effective strategy. Threshold analyses show that the test must be highly accurate (especially sensitive) and inexpensive to be the most cost-effective strategy, since myopathy has a negligible impact on cost effectiveness and statin costs are low.

Conclusion: Use of a highly accurate prognostic test could reduce overall CVD risk, frequency of drug side-effects and lifetime costs. However, no additional test would add usefully to risk prediction over SCORE when it does not satisfy the costs and accuracy requirements.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death across Europe and one of the major causes of disability[16]. Due to its high prevalence and morbidity rate, the economic burden of CVD is also substantial. Means to prevent CVD include lifestyle modification and medicines such as statins[17,18]. Although the annual costs of generic statins per individual are low, the budgetary impact of wide-scale statin usage is substantial due to the high prevalence and lifetime utilization. Since preventive statin treatment is associated with some risk, e.g. myopathy, the use of statins is not cost-effective in individuals at low risk[19]. In subjects at higher risk, however, the issue may be quite different.

Risk scores such as the Framingham risk score (FRS)[9] and the Systematic coronary risk evaluation (SCORE) method[7] are well-accepted tools to estimate the 10-year risk of (non-) fatal CVD and decide which individuals qualify for statin treatment. The most recent 2012 European guidelines[20] make use of the SCORE, which categorises individuals into three risk categories (low, intermediate, high). Individuals at intermediate risk with an elevated cholesterol level are recommended to receive statin therapy. However, only 3–15% of them actually develop a cardiovascular event. In theory, tests could potentially be used to reclassify some of these intermediate-risk individuals into a lower or higher risk category[21], with subsequent implications for their medical treatment. This would lead to better discrimination and thus a reduction in costs and an increase in effectiveness since cardiovascular events and unnecessary usage of statins would be prevented. However, the discriminative ability of biomarkers such as C-reactive protein beyond traditional markers (SCORE) is only modest[22]. The limited prognostic value of the risk scores and traditional markers as well as the rapid increase in the prevalence of CVD risk factors necessitates the development of other strategies to predict and prevent the development of CVD.

Therefore, the aim of our study was to use the 10 year SCORE risk to estimate the potential 10-year cost-effectiveness of a (theoretical) test compared with a treat-none strategy, treat-all strategy, and a strategy based on European guidelines. In addition, we examined the conditions (accuracy estimates and costs) under which the use of a novel test (e.g. biomarker) would be cost-effective.

METHODS

The cost-effectiveness of a test was estimated for eight age- and gender-specific cohorts of individuals with an intermediate risk (3–15%) of developing a first-time CVD event in the next 10 years[20]. The SCORE risk equation was used to identify individuals with an intermediate risk based on age, gender, systolic blood pressure, total cholesterol and smoking status. SCORE risk

estimates were multiplied by a factor of three to obtain the risks of non-fatal and fatal events, as proposed by the European Society of Cardiology (ESC) guidelines[20]. We subsequently modelled the prognosis of eight cohorts, defined by the SCORE, of men and women with an age of 50, 55, 60, and 65 years.

Strategies

We compared the costs and effectiveness of four strategies: 1) "treat-all" strategy, where all individuals receive statin treatment; 2) a "treat-none" strategy, where none of the individuals receive statin treatment, 3) a "guidelines" strategy, where individuals receive statin treatment according to the ESC guidelines on CVD prevention[20] (which recommend that statins should only be given to those with total cholesterol level ≥5 mmol/L and/or low-density lipoprotein cholesterol level ≥3 mmol/L) and 4) a "test-first" strategy, where statin treatment is recommended for individuals having a positive test result. A positive test result suggests that a first-time CVD event in the next 10 years will occur if statin treatment is not provided.

Model structure

For each strategy, the prognosis of a cohort of individuals for the next 10 years was modelled in a Markov model (Microsoft Excel™ 2010) with eight health states (Figure 2.1). A time horizon of 10 years was chosen since the SCORE only provides an accurate estimate of 10-year risks. All individuals started in the "intermediate risk" state and annual transition probabilities determined the likelihood of moving to other health states (Table 2.1). Individuals experiencing a non-fatal CVD event (myocardial infarction (MI), stroke or revascularization) or a statin-induced non-fatal adverse event (myopathy) moved to the post-event states afterwards the event. Individuals experiencing cardiovascular or non-cardiovascular fatal events moved to the absorbing health states "cardiovascular death" and "non-cardiovascular death", respectively. In all strategies, individuals experiencing a cardiovascular event received statin treatment afterwards. Statin treatment was discontinued permanently if individuals developed myopathy and its discontinuation also meant loss of the protective effects of the statins.

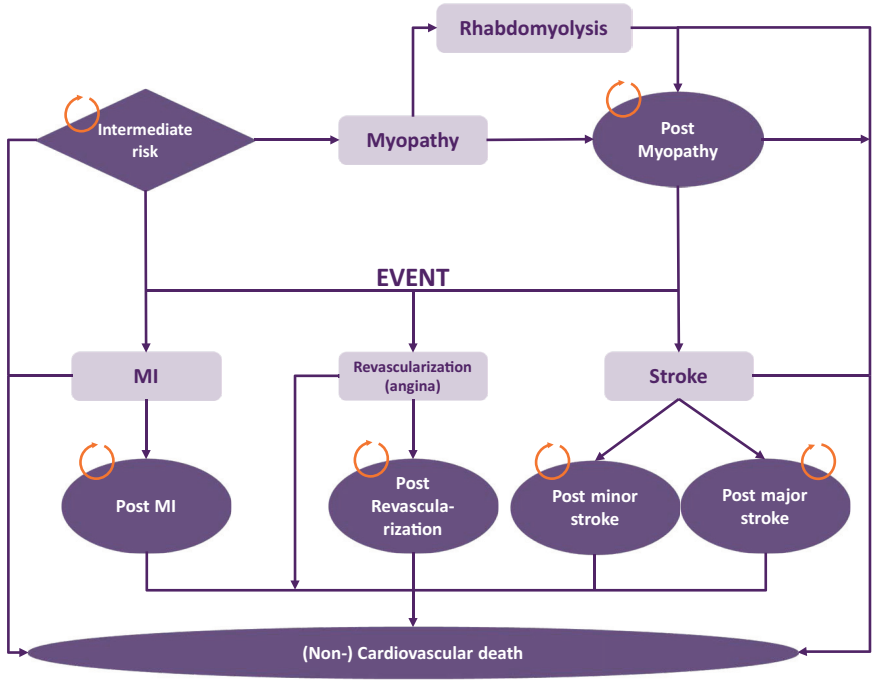

Figure 2.1 | Model structure*

*Cardiovascular death and non-cardiovascular death are presented as one state in this Figure. Rectangles are (non) cardiovascular events and ovals are disease states. MI, myocardial infarction.

Input parameters

A literature search using PubMed was performed to obtain input values. Table 2.1 shows the input parameters for the subgroup of men aged 65 years, illustrative for the eight cohorts that were modelled.

a | *Risks*

The risk of developing (non-) fatal CVD events (MI, stroke, angina-induced revascularization and cardiovascular death) was obtained from the SCORE chart by taking the average of all possible combinations with an intermediate risk in each gender- and age-specific cohort. Based on the randomized controlled trials (RCTs) included in the meta-analysis of Brugts et al.[18] we divided the individuals treated according to the guidelines into two groups: 1) individuals with elevated cholesterol levels, indicated for statin treatment and 2) individuals with normal cholesterol levels. We assumed that individuals with normal cholesterol levels had the lowest possible intermediate risk of CVD in their respective gender- and age-specific cohort (appendix). In our analyses, individuals with elevated cholesterol levels were assigned inherently higher risk than the average intermediate risk in the same gender- and age-specific cohort to ensure that the

average risk remained unchanged when the two groups were combined. A meta-analysis[18], UK audit data[23], the FRS[9] and three RCTs[24-26] were used to estimate age- and gender-specific relative proportions of the CVD events. The annual probabilities of developing myopathy and (non-) fatal rhabdomyolysis caused by statins were based on Law et al.[27]. Mortality was based on national and international mortality statistics[23,28-32].

The sensitivity and specificity of the hypothetical test were both assumed to be 100% in the base-case scenario and the impact of their values was explored through sensitivity analyses. Therefore, in the base-case scenario it is assumed that the test will discriminate absolutely and perfectly all individuals who will experience a cardiovascular event over the specified time period and those who will not.

Table 2.1 | Input data used in the Markov model (men 65 year)

	Base-case value	Distribution	Reference
Parameters			
Probabilities of (non-) cardiovascular events*			
10-year risk of event (myocardial infarction, stroke, revascularization or cardiovascular death)	0.107		7
Annual risk of event (myocardial infarction, stroke, revascularization or cardiovascular death)	0.0113		7
Myocardial Infarction	0.0061	Beta	9
Mortality (first year)	0.1530	Beta	29
Mortality (subsequent years)	0.0343	Beta	29
Stroke	0.0030	Beta	9
Fatal	0.12	Beta	24-26
Minor stroke vs. major stroke	0.80	Beta	Assumption
Revascularization	0.0022	Beta	18,23
Fatal	0.0064	Beta	23,31,32
Non-cardiovascular death	0.0125	Beta	28
Treatment effectiveness of statins			
RR of non-fatal myocardial infarction, statins vs. placebo	0.56	Lognormal	18
RR of revascularization, statins vs. placebo	0.67	Lognormal	18
RR of stroke, statins vs. placebo	0.81	Lognormal	18
Myopathy	0.00011	Beta	27
Rhabdomyolysis	0.31	Beta	27
Diagnostic accuracy of the biomarker			
Sensitivity	100%	Beta	Assumption
Specificity	100%	Beta	Assumption
Proportion of patients with elevated cholesterol	0.82	Beta	26,33-36

Table 2.1 | *(Continued)*

	Base-case value	Distribution	Reference
Costs (€)			
Biomarker test	250	Gamma	Assumption
Costs of events, first year			
Myocardial infarction	4873	Gamma	[37]
Myopathy	166	Gamma	[27,38,39]
Minor stroke	8494	Gamma	[40]
Major stroke	18,084	Gamma	[40]
Revascularization	12,426	Gamma	[32,41]
Costs of events (annual), subsequent years			
Myocardial infarction	2708	Gamma	[42]
Minor stroke	2722	Gamma	[40]
Major stroke	3924	Gamma	[40]
Costs of fatal events			
Myocardial infarction	1834	Gamma	[42]
Stroke	11,618	Gamma	[40]
Revascularization	8293	Gamma	[41]
Costs of statin therapy			
Statin treatment (simvastatin 40mg/d)	17	Gamma	[43]
Doctor visits (4 visits)	35	Gamma	[44]
Utilities			
Healthy	0.86	Beta	[41]
Post-myocardial infarction	0.86	Beta	[41]
Post-major stroke	0.32	Beta	[45]
Post-minor stroke	0.71	Beta	[45]
Post-revascularization	0.86	Beta	[41]
Disutility myopathy	-0.1	Beta	Assumption
Disutility minor stroke	-0.1	Beta	Assumption
Disutility major stroke	-0.3	Beta	Assumption
Disutility revascularization (angina)	-0.0825	Beta	[41]
Disutility myocardial infarction	-0.0825	Beta	[41]

RR: Relative risk; vs: versus; * Annual probabilities

b | Cost, treatment effectiveness and quality of life

The impact of changes in 10-year risks of CVD events was translated into costs and quality-adjusted life-years (QALY). Costs (€2012) and QALYs were estimated from a health care sector perspective and discounted at 4% and 1.5%, respectively, in accordance with Dutch guidelines[46]. Costs were converted to the price year 2012 using consumer price indices and inflation corrections if necessary[47,48].

The cost of the hypothetical test was initially set at €250 in the base-case scenario and the cost of statin treatment was based on Dutch wholesale prices[43,44]. Costs of events were based on recent cost-effectiveness and cost-of-illness studies[37-42,49]. Treatment effectiveness of statins was based on a recently published meta-analysis[18] and, based on this meta-analysis, treatment effectiveness was assumed to be independent of age, gender and risk since differences between the groups were non-significant. Because costs for yearly doctor visits were included, the adherence rates (80–90%) were assumed to be comparable to statin trial results[50,51]. Quality-of-life values were derived from two studies[41,45].

We estimated the differences in costs and effectiveness (QALYs) between the four strategies and arranged them according to increasing effectiveness. Where possible, we also calculated incremental cost-effectiveness ratios (ICER).

Additional analyses

Additional analyses were performed to determine how much the uncertainty about the values of input parameters influenced the results. Probabilistic sensitivity analysis (PSA), where the values of many input parameters are varied simultaneously, was also performed. The test sensitivity and specificity were varied between 90% and 100% (in steps of 5%). Threshold analyses were performed to determine the maximum price and minimal diagnostic performance (sensitivity and specificity) of a test that were possible while ensuring that the test-first strategy was the most cost-effective strategy; i.e., either cost-saving and more effective or cost-effective given a willingness-to-pay (WTP) of €50,000. In addition, scenario analyses were performed to assess the impact of: 1) reducing the effectiveness of statin treatment; 2) including the inconvenience (disutility) of taking statins; 3) higher statin treatment costs; 4) greater health loss (disutility) from myopathy; and 5) increasing the time horizon from 10 years to 20 years.

RESULTS

The base-case results of the four strategies for all cohorts are presented in Table 2.2 and Figure 2.2. For all strategies, mean costs increased and mean QALYs decreased as age increased (and thereby also 10-year CVD risk). In all cases, the treat-none strategy was the least effective strategy, followed by the guidelines strategy, treat-all strategy, and the test-first strategy. The test-first strategy was also the least expensive strategy for most of the cohorts, making it the dominant strategy since it reduced costs and increased effectiveness. The only exception was for the cohort of 50-year old women, where the treat-none was the least expensive strategy due to the very low risk (about only 4.3%) of developing a cardiovascular event. Furthermore, the guidelines strategy was less effective than the treat-all strategy although in almost all cohorts cost-saving. Overall, the test-first strategy resulted in a marginal QALY gain of 0.0002 and a cost-savings of €128 per individual over a 10-year period versus the treat-all strategy. Figure 2.3 presents the cumulative

costs for each strategy (for 65 year old men) and shows that the test-first strategy becomes less expensive than the other strategies after approximately 7 years.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis revealed that the test-first strategy had the highest probability of being the most cost-effective strategy, regardless of the WTP since the incremental effectiveness versus the treat-all strategy is very small.

Threshold analyses

The test-first strategy remained the dominant choice for all cohorts as long as the perfect test cost no more than €237. When the price of the test was set at €250, the test had to have a sensitivity and specificity of at least 94% to be cost-effective at a willingness-to-pay of €50,000 euro per QALY gained. Figure 2.2 shows the influence of changes in test accuracy on the costs and effectiveness of the test-first strategy. A decrease in specificity leads to an increase in false positives, resulting in a higher frequency of unnecessary statin treatment. The solid arrow (purple) shows that reduced specificity increases the total costs of the test-first strategy; when the specificity is zero, the test-first strategy is more expensive – and therefore less cost-effective – than the treat-all strategy. Note that since the side-effects of statin treatment are rare and minimal, this solid arrow is almost vertical. The impact of a decrease in sensitivity is shown by the dash-dotted arrow (green). Reduced sensitivity is associated with an increase in false negatives, meaning that some individuals who have a negative test result will experience a CVD event in the next 10 years if they are not treated with statins. Reduced sensitivity makes the test-first strategy more costly and less effective since some individuals do not receive beneficial statin treatment. The test-first and treat-none strategies are equally effective when the sensitivity is 0% and specificity is 100%, since the test is negative in all individuals and no complications are associated with the test itself. However, the costs of the test-first strategy are higher than the treat-none strategy because of the costs of the test. The dashed line (blue) shows how an equal decrease in the sensitivity and specificity of the test affects the results and demonstrates that the sensitivity has more influence on the cost-effectiveness of the test-first strategy than specificity.

Scenario analyses

Use of a 20-year time horizon increases the relative effectiveness and cost-savings potential of a test-first strategy since the benefits of preventing CVD and unnecessary statin treatment were extended for a longer period.

As presented in Table 2.3, the addition of disutility for statin use (reflecting the inconvenience of taking statins daily) improved the effectiveness and cost-effectiveness of the test-first strategy since this strategy ensures that only individuals who will benefit from statin treatment are treated. The use of disutility increased the maximum possible price of the test to €742 at a threshold of €50,000 per QALY gained. Besides this effect, the overall findings did not change.

Table 2.2 | Cost-effectiveness of different CVD prevention strategies (base-case results)

Cohort									
Gender	**Age**	**SCORE**	**Strategy**	**QALYs**	**Δ QALYs**	**Costs (€)**	**Δ Costs (€)**	**Incremental cost-effectiveness ratio (€ per QALY gained)**	**Threshold analysis (€)***	**Threshold analysis (€)****
Men	50	7.2%	Treat-none	7.719		1,158				
			Guidelines	7.729	0.01042	1,138	-20	Dominates Treat-none		
			Treat-all	7.730	0.00077	1,172	34	44,566 (vs. Guidelines)		
			Test-first	7.730	0.00023	1,033	-139	Dominates all	354	400
	55	8.6%	Treat-none	7.607		1,351				
			Guidelines	7.620	0.01331	1,258	-93	Dominates Treat-none		
			Treat-all	7.621	0.00069	1,296	38	55,602 (vs. Guidelines)		
			Test-first	7.621	0.00022	1,167	-128	Dominates all	340	385
	60	10.5%	Treat-none	7.437		1,589				
			Guidelines	7.453	0.01577	1,425	-164	Dominates Treat-none		
			Treat-all	7.454	0.00137	1,446	21	15,497 (vs. Guidelines)		
			Test-first	7.454	0.00021	1,332	-114	Dominates all	343	374
	65	10.7%	Treat-none	7.204		1,586				
			Guidelines	7.219	0.01512	1,441	-145	Dominates Treat-none		
			Treat-all	7.221	0.00218	1,441	-1	Dominates Treat-none & Guidelines		
			Test-first	7.221	0.00020	1,338	-103	Dominates all	353	363

Table 2.2 | *(Continued)*

Cohort

Gender	Age	SCORE	Strategy	QALYs	Δ QALYs	Costs (€)	Δ Costs (€)	Incremental cost-effectiveness ratio (€ per QALY gained)	Threshold analysis (€)*	Threshold analysis (€)**
Women	50	4.3%	Treat-none	7.774		759				
			Guidelines	7.778	0.00389	892	133	34,296		
			Treat-all	7.779	0.00076	924	32	41,913 (vs. Guidelines)		
			Test-first	7.779	0.00024	772	-152	Dominates Treat-all & Guidelines	237	414
	55	6.1%	Treat-none	7.687		1,031				
			Guidelines	7.695	0.00851	1,074	43	5,096		
			Treat-all	7.696	0.00077	1,109	35	45,408 (vs. Guidelines)		
			Test-first	7.696	0.00023	968	-141	Dominates all	313	403
	60	7.5%	Treat-none	7.585		1,233				
			Guidelines	7.597	0.01168	1,216	-17	Dominates Treat-none		
			Treat-all	7.597	0.00083	1,252	36	43,092 (vs. Guidelines)		
			Test-first	7.598	0.00022	1,120	-132	Dominates all	346	393
	65	9.5%	Treat-none	7.429		1,524				
			Guidelines	7.445	0.01619	1,428	-96	Dominates Treat-none		
			Treat-all	7.446	0.00120	1,458	30	24,940 (vs. Guidelines)		
			Test-first	7.447	0.00021	1,341	-118	Dominates all	338	378

* Maximum price if the willingness to pay is set at €0 per QALY gained

** Maximum price if the willingness to pay is set at €50,000 per QALY gained

QALY: quality-adjusted life-years

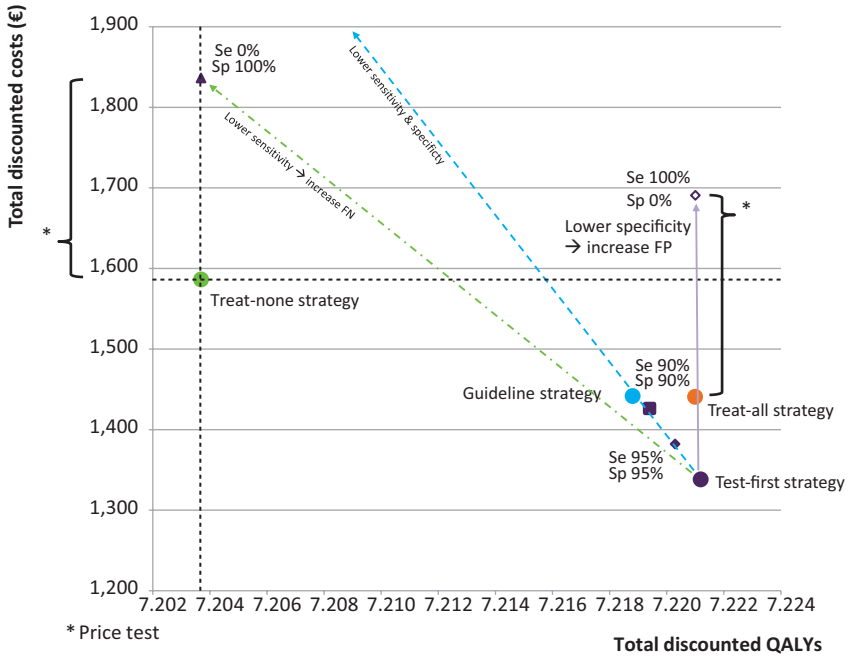

Figure 2.2 | Cost-effectiveness plane for 65-year old men†

* Price of the test

† The treat-none strategy is considered as the comparator

Se: sensitivity; Sp: specificity; QALYs: quality-adjusted life years; FP: false positives; FN: false negatives

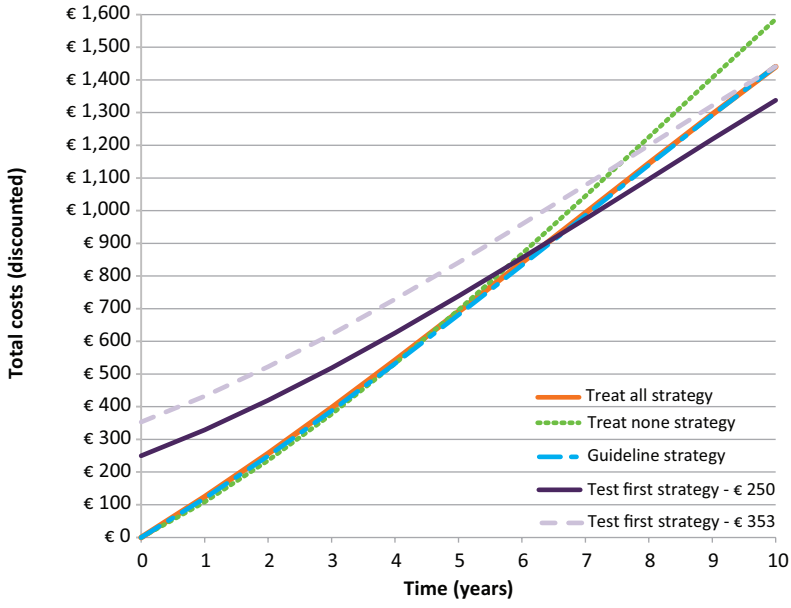

Figure 2.3 | Cumulative costs of the strategies for 65-year old men*

* Discounted at 4%

Table 2.3 | Cost-effectiveness of different CVD prevention strategies (Scenario analyses 65 year old men)

Scenario	Strategy	QALYs	Δ QALYs	Costs (€)	Δ Costs (€)	Incremental cost-effectiveness ratio (€ per QALY gained)	Threshold analysis (€)*	Threshold analysis (€)**
Base-case	Treat-none	7.204		1,586				
	Guidelines	7.219	0.015	1,441	-145	Dominates Treat-none		
	Treat-all	7.221	0.002	1,441	-1	Dominates Treat-none & Guidelines		
	Test-first	7.221	0.000	1,338	-103	Dominates all	353	363
Presence of disutility from daily statin use	Treat-none	7.204		1,586				
(-0.001)	Guidelines	7.212	0.008	1,441	-145	Dominates Treat-none		
	Treat-all	7.213	0.001	1,441	-1	Dominates Treat-none & Guideline		
	Test-first	7.220	0.008	1,338	-103	Dominates all	353	742
Higher costs of statins	Treat-none	7.204		1,586				
(Most expensive drug at €40 per year)	Guidelines	7.219	0.015	1,574	-12	Dominates Treat-none		
	Treat-all	7.221	0.002	1,603	29	13186 (vs. Guidelines)		
	Test-first	7.221	0.000	1,349	-254	Dominates all	475	514
Higher disutility from myopathy	Treat-none	7.204		1,586				
(-0.30)	Guidelines	7.219	0.015	1,441	-145	Dominates Treat-none		
	Treat-all	7.221	0.002	1,441	-1	Dominates Treat-none & Guideline		
	Test-first	7.221	0.000	1,338	-103	Dominates all		375
Reduced statin efficacy	Treat-none	7.204		1,586				
(Upper bound of 95% confidence interval for relative risk)	Guidelines	7.211	0.007	1,641	55	7,716		
	Treat-all	7.212	0.001	1,669	28	25770 (vs. Guidelines)		
	Test-first	7.212	0.000	1,566	-103	Dominates all		363

* Maximum price at a willingness to pay set of €0 per QALY gained
** Maximum price at a willingness to pay set of €50,000 per QALY gained
QALY: quality-adjusted life-years; RR: relative risk

DISCUSSION

The recently introduced European guidelines[20] recommend statins for individuals at moderate risk of fatal CVD events and elevated cholesterol levels. Consequently, many individuals with intermediate risk are treated with statins even though only one in every 7–33 individuals will actually develop a CVD event in the next 10 years.

As could be expected, the results of this cost-effectiveness analysis show that the guidelines strategy is a more favourable option than the treat-none strategy. Moreover, after a 4-year period the guidelines strategy becomes less expensive and avoids more cardiovascular events than the treat-none strategy. Furthermore, the guidelines strategy is less expensive than and just as effective as the treat-all strategy in almost all cohorts. However, the guidelines strategy and treat-all strategy both lead to unnecessary statin-induced myopathy events and costs. In theory, these can be prevented by using a test to identify individuals who would actually benefit from statin treatment. A strategy incorporating a prognostic test (e.g. biomarker) can be more cost-effective than other strategies, including the current European guidelines. However, the test must fulfil certain conditions relating to price and diagnostic accuracy. The test-first strategy using a test with 100% accuracy would be more cost-effective than the guidelines strategy as long as the price of the test does not exceed €385 given a willingness to pay of €50,000 per QALY gained. A test-first strategy is cost-effective only if the diagnostic accuracy of the test is very high; the test's sensitivity is more important than its specificity. It is important to recognize that these estimates are reasonably high (90–100%). Currently available tests rarely have these levels in any area in cardiology but based on the sensitivity analyses a test with lower sensitivity and specificity values were considered not cost-effective. Note that most test results are measured on a continuous scale and consequently the positivity criterion (cut-off) determines the sensitivity and specificity of the test. Dichotomizing test results on a continuous scale often leads to a trade-off between maximising sensitivity and specificity.

Interestingly, in the present study we investigated the cost-effectiveness of a hypothetical test. In fact, this could be any test that adds information to the SCORE method such as an imaging result (e.g. CT coronary calcium score or a coronary angiogram), a biomarker test (e.g. C-reactive protein) or a physiological test (e.g. a treadmill or a stress echo). Our results are important because for any test performed to reclassify/discriminate intermediate risk individuals, we provide a maximal price or minimal accuracy in order for it to be cost-effective.

A recent study investigated the cost-effectiveness of statins in primary prevention of CVD for individuals at different levels of risk[19]. This study found that the treat-all strategy was more expensive than the treat-none strategy due to higher annual costs of statin therapy (€157). We found comparable results in the lower risk cohorts (men of 50 years of age and women 50–60

years). However, use of the same annual costs of statins leads to the same result in the higher risk cohorts in our study and the incremental effectiveness the authors reported is comparable with our result. Another study of individuals at intermediate risk estimated the cost-effectiveness of a computed tomography (CT) scanner as an additional reclassification method and compared it with American Heart Association guidelines, current practice and treating all individuals with statins and aspirin[52]. In their study, the CT scanner was the most effective strategy. The reported incremental QALYs were larger than in our study; one explanation could be that both aspirin-related and statin adverse events were included.

Strengths and limitations

Our model provides an accurate representation of the clinical pathways for individuals at CVD risk. For instance, the model used in our study included the costs and consequences of angina-related revascularizations, myopathy and rhabdomyolysis. When these costs are also considered, the test-first strategy is more cost-effective than alternative strategies even though all patients must undergo the test. Our study does not incorporate other adverse events of statin intake such as liver damage. However, the incidence of liver damage is extremely low and probably not much different than that of individuals not taking statins[27]. Consequently, its inclusion would only marginally reduce the estimated effectiveness of strategies that include statin treatment.

Unlike other studies, we based CVD event rates on the SCORE method, which is more appropriate than estimates derived from studies not focusing on intermediate-risk populations. However, the risks found in the SCORE are based on several sources from 12 European countries and therefore not specific for the Netherlands. It is also known that the SCORE risk equation overestimates the actual risk of fatal CVD events in some populations[53]. Since we selected individuals from the SCORE chart with an intermediate risk (3%–15%), this limitation does not apply to our results. Furthermore, we used a multiplier to obtain the risk of fatal and non-fatal cardiovascular events. This multiplier, proposed in the European guidelines, may actually be somewhat smaller in older individuals. Therefore, our results might not be fully applicable in older patients with a relatively low SCORE risk. The health gain from statin intake amongst these patients could therefore be overestimated; this would mean that the cost-effectiveness for treat-all, test-first and the guidelines vs. treat-none strategy is less favourable than what we estimated.

In our study, the decision about statin treatment was based only on the estimated CVD risk at baseline. However, it is likely that some individuals not treated at baseline will receive statins after a few years because of an increase in their estimated CVD risk. This phenomenon would mean a gradual increase in statin use in the guidelines strategy, which might improve its effectiveness and perhaps also reduce the estimated costs. Lack of detailed data about temporal changes in CVD risk made it impossible to incorporate later statin initiation in the analyses. Furthermore, we also assumed that the test accurately determines which individuals would benefit from treatment for

a time horizon of ten years and therefore assumed that testing once at baseline was sufficient. However, it is possible that testing should be repeated every year. Since the threshold analysis revealed the maximum possible price for one test in a 10-year time horizon, the strategy of regular testing would reduce the maximum acceptable price per test proportionally.

Implications

One potential benefit of a CVD prediction test would be to reduce the frequency of myopathy by treating only individuals with a high CVD risk. However, the health gain is very small since statin use is associated with only a small risk of myopathy. Another value of a test from a patient perspective would be that patients would have a better idea of their CVD risk and that patients with a negative test result could be reassured that their chances of developing CVD in the next 10 years will be very small. While this 'peace of mind' is not included in the current way of quantifying effectiveness, it has been identified as another dimension in the assessment of tests[54]. In addition, it is possible that individuals who become more aware of their high risk would improve their lifestyle (e.g. smoking cessation or dietary changes), which would further reduce their risk of CVD events and increase the effectiveness of the test-first strategy beyond what would be expected based on statin use alone. Furthermore, if statin use is associated with disutility its use could be limited to the individuals who would benefit from it. From a clinician's perspective, the foremost goal is to ensure that patients receive the best possible treatment, which would mean choosing the most effective strategy available. Based on our results, this would be either the treat-all strategy or the test-first strategy in most cases. However, when the problem is viewed from a payer perspective, a test-first strategy might provide a way to reduce the long-term budget impact of statin use without placing patients at unnecessary risk of CVD (Figure 2.3), as long as the test sensitivity and specificity are sufficiently high. However, the payer would have to be willing to accept the higher short-term costs of using the test-strategy (mainly because of the costs of the test) versus the treat-none strategy. The same trade-off holds true for treating all patients with statins or applying the guidelines versus treating no patients with statins; both strategies will increase short-term costs because of statin use.

Conclusions

There is a large population of individuals with an intermediate CVD risk who may benefit from statin treatment. A test capable of stratifying individuals in this population into lower and higher risk groups has the potential to be cost-effective versus alternative strategies as long as it is not too expensive and its diagnostic accuracy is high. In particular, a test with a sufficiently high sensitivity would have the potential to be more effective and cost-saving than the strategy proposed in the European guidelines and the more extreme treat-all strategy. No additional test would add usefully to risk prediction over SCORE or similar risk scores when it does not satisfy the costs and accuracy requirements given the effectiveness and relatively low costs of currently available statins.


Challenges
Modelling
Cardiovascular
Technologies
Devices
Tests
ICER
QALY
Blood
Data
CVD
Results
Analyses
Markov
Cost-effectiveness
Disease
Extrapolating
Costs
Thesis
Angina
CAD
PCI
Drugs
Diagnosis

Chapter 3

Cost-effectiveness analysis of new generation coronary CT scanners for difficult to image patients

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Westwood ME
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Submitted, based on Chapter 4 of
Westwood ME, Al MJ, Burgers LT, Redekop WK, Lhachimi SK, Armstrong N, et al. A systematic review and economic evaluation of new-generation computed tomography scanners for imaging in coronary artery disease and congenital heart disease: Somatom Definition Flash, Aquilion ONE, Brilliance iCT and Discovery CT750 HD. Health Technol Assess 2013;17(9)

ABSTRACT

Aims: New generation dual-source coronary CT (NGCCT) scanners with more than 64 slices were evaluated for patients with (known) or suspected of coronary artery disease (CAD) who are difficult to image: obese, coronary calcium score >400, arrhythmias, previous revascularization, heart rate >65 beats per minute, and intolerance of beta-blocker. A cost-effectiveness analysis of NGCCT compared with invasive coronary angiography (ICA) was performed for these difficult to image patients for England and Wales.

Methods and results: Five models (diagnostic decision model, 4 Markov models for CAD progression, stroke, radiation and healthy person) were integrated to estimate the cost-effectiveness of NGCCT for both suspected and known CAD populations. The lifetime costs and effects from the National Health Service perspective were estimated for three strategies: i) patients diagnosed using ICA, ii) using NGCCT, and iii) patients diagnosed using a combination of NGCCT and in case positive, followed by ICA. In the suspected population, the strategy where patients only undergo a NGCCT is a cost-effective option at accepted cost-effectiveness thresholds. The strategy NGCCT in combination with ICA is the most favourable strategy for patients with known CAD. The most influential factors behind these results are the percentage of patients being misclassified (a function of both diagnostic accuracy and the prior likelihood), the complication rates of the procedures, and the cost price of a NGCCT scan.

Conclusion: The use of NGCCT might be considered cost-effective in both populations since it is cost-saving compared to ICA and generates similar effects.

INTRODUCTION

In recent years imaging technologies have been developed rapidly leading to the introduction of new generation coronary computed tomography (NGCCT) scanners. The latest generation of dual-source instruments may have a significant benefit over the current technologies, especially for difficult-to-image patients through improvements in image quality, and reductions in the scan duration and radiation exposure.

Currently, for patients suspected of coronary artery disease (CAD) the diagnosis is usually based on tests such as an invasive coronary angiography (ICA), functional imaging, computed tomography (CT) coronary angiography (CTCA), or a computed tomography calcium scoring. The appropriate diagnostic test depends on the likelihood of having CAD[10]. Furthermore, these diagnostic tests can also be used to decide if a revascularization is necessary. The performance of 64-slice CT for diagnosing CAD has been well established. Recent systematic reviews have estimated that 64-slice CT, for the detection of ≥50% coronary artery stenosis, is very accurate[55-57]. However, 64-slice CT cannot be (routinely) used for specific groups of patients who are difficult to image due to decreased image quality[58]. These include patients with: i) arrhythmias, ii) heart rate >65 beats per minute, iii) obesity, iv) coronary calcium level >400, v) a previous coronary revascularisation with a stent, vi) β-blocker intolerance or vii) a previous coronary artery bypass graft (CABG). In these difficult-to-image patients, ICA a more invasive diagnostic procedure may therefore be indicated. Newer generation CT instruments may provide an alternative to an ICA for these patients, which has a lower procedure-related mortality and morbidity. One potential disadvantage may be a slightly lower sensitivity and specificity compared to ICA, which means a greater frequency of false positive (FP) and false negative (FN) results that may lead to incorrect treatment decisions, health loss and increased costs. We performed a cost-effectiveness study of the NGCCT compared with ICA for difficult-to-image patients for England and Wales.

METHODS

The lifetime cost-effectiveness of NGCCT for difficult-to-image patient groups was estimated for two separate populations: patients with suspected CAD and patients with known CAD. The suspected CAD population includes patients with chest pain or other symptoms suggestive of CAD. Patients with known CAD were defined as patients with a diagnosis of CAD whose symptoms are no longer controlled with drug treatment and/or are being considered for revascularization. The characteristics (e.g. age, systolic blood pressure) of the difficult-to-image subgroups are based on the studies that are included in a systematic review[32]. The NGCCT has a different purpose in each population: diagnose CAD in the suspected population or decide if revascularization is necessary in the known CAD population.

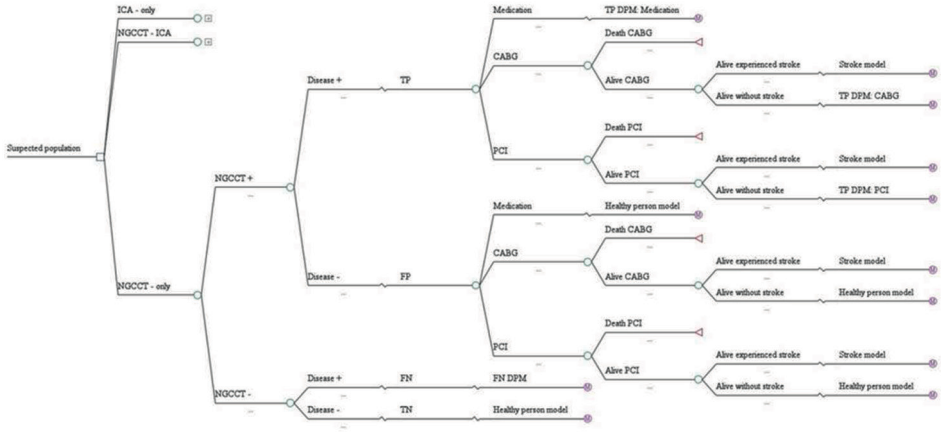

Figure 3.1 | Diagnostic model for suspected CAD population

CAD: coronary artery disease; ICA: invasive coronary angiography; NGCCT: new generation coronary computed tomography; TP: true positive; FP: false positive; FN: false negative; TN: true negative; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; DPM: disease progression model

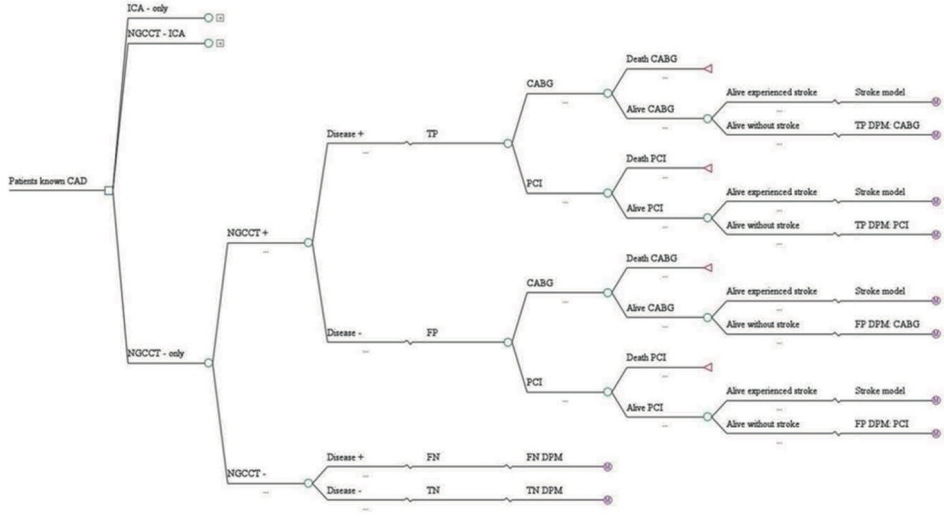

Figure 3.2 | Diagnostic model for known CAD population

CAD: coronary artery disease; ICA: invasive coronary angiography; NGCCT: new generation coronary computed tomography; TP: true positive; FP: false positive; FN: false negative; TN: true negative; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; DPM: disease progression model

Strategies

Three strategies were examined: i) a strategy where patients only undergo an ICA (ICA–only strategy), ii) a strategy where patients only undergo the NGCCT (NGCCT–only strategy), and iii) a strategy where patients are first assessed with NGCCT and undergo an ICA if the NGCCT is positive (NGCCT–ICA strategy). NGCCTs are defined as dual-source cardiac CT scanners with >64 slices (Brilliance iCT (Phillips Healthcare), Somatom Definition Flash (Siemens Healthcare), Aquilion ONE (Toshiba Medical Systems), and Discovery CT750 HD (GE Healthcare)).

Models

The cost-effectiveness analyses were conducted by combining five models: i) a decision model of the diagnostic pathway (diagnostic model)[59], ii) a Markov model reflecting the prognosis of CAD patients (disease progression model (DPM)[60]), iii) a Markov model to estimate the impact of radiation on cancer mortality and morbidity (adjusted York radiation model (YRM)[32,61]), iv) a Markov model to account for mortality amongst persons without CAD (healthy person model (HPM)[59]), and v) a Markov model to estimate the impact of stroke due to the initial test and treatment (stroke model). The diagnostic model (Figure 3.1 and Figure 3.2), where the entire cohort of patients starts, splits up the cohort based on diagnostic performance, complication rates and prior likelihood. For example, the proportion with a true positive (TP) test was modelled with the DPM (Figure 3.3) and the proportion of patients experiencing a stroke due to ICA was modelled with the stroke model. At the end we combined all the proportions modelled through one of the five models with their outcomes leading to a total cost-effectiveness estimate for each specific difficult-to-image subgroup. However, the aim was to compare the overall cost-effectiveness of the three strategies in each of the two populations (suspected and known CAD). Expert opinion was used to gather information on the relative frequencies of patients (Tables 3.2 and 3.3) in the difficult-to-image subgroups in the known or suspected CAD population. Multiplication of the relative proportions with the subgroup-specific costs and effects produced an overall ICER for both populations.

The analyses were based on cohort simulations. Costs and effects were discounted at 3.5%, and the study was performed from a National Health Service perspective.

Model variables

Input parameters, based on published literature and expert opinion, are provided as supplementary data in Table S3.1.

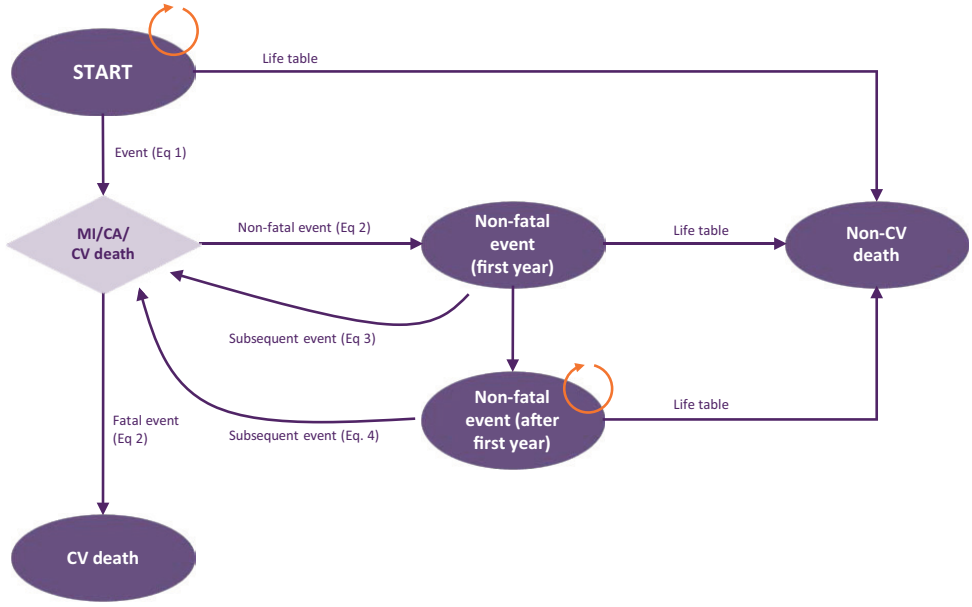

Figure 3.3 | Disease progression model*

* Adapted from Briggs et al. 2007[60]
MI: myocardial infarction; CA: cardiac arrest; CV: cardiovascular; Eq: equation

Transition probabilities

Prior likelihood, accuracy estimates of the tests and complication rates of the procedures are important parameters in the diagnostic model. The prior likelihood (20%) of having CAD in patients with suspected CAD was based on the clinical guideline "Chest pain of recent onset"[10]. Patients with a prior likelihood of 20% are normally diagnosed with a 64-slice CT, the technology that the NGCCT will replace for patients who are difficult to image. The prior likelihood of performing a revascularisation in patients with known CAD was based on the CE-MARC study[59] (Table S3.1). We used this estimate due to lack of data despite the possibility that the CE-MARC population may not perfectly match our population. The sensitivity and specificity of ICA were assumed to be 100%, as in Mowatt et al.[55]. The estimates of the sensitivity and specificity for the NGCCT were based on a systematic review which aimed to identify accuracy estimates for all type of scanners[62]. This review found 21 studies evaluating the Somatom definition (flash), one study evaluating the Aquilion ONE and one study evaluating the Discovery CT750 HD. In the remainder of the paper we will assume that these accuracy estimates are generalizable to other NGCCTs. Complication rates of ICA and the procedures were based on West et al.[63], Tarakji et al.[64], Serruys et al.[65], Rajani et al.[66], and Bridgewater et al.[67].

The risks of cardiovascular events for patients with CAD in the DPM were based on the results of the EUROPA trial[60]. We used four equations to calculate: i) the probability of any event that will occur in one cycle of three months; ii) the probability that the event is fatal; iii) the probability of a subsequent event in the first year after a first non-fatal event; and iv) the probability of a subsequent event after one year.

Life expectancy for patients without CAD was based on UK life tables[68]; the life expectancy for stroke patients was derived by adjusting the UK life tables for excess mortality risk based on an observational study of stroke patients[30].

The adjusted version of the YRM models the harmful consequences of radiation exposure. Based on age at exposure, gender, and radiation dose (mSv) we have estimated the probability of developing cancer. For patients developing radiation-induced cancer, the remaining quality-adjusted life-years (QALYs) given the average age of cancer incidence and the average treatment cost for cancer are calculated[61].

Costs

The costs of the three strategies included the cost of the diagnostic tests, non-fatal events (myocardial infarction (MI) and cardiac arrest), procedures (e.g., revascularisation), CAD management costs (e.g. medication), stroke-related costs and costs due to radiation-induced cancer (Table S3.1). Original cost prices were inflated to reflect costs for 2010 using PSSRU Health Unit costs of Health and Social Care 2010[69].

The cost of the NGCCT procedure was calculated using a bottom-up costing since only data for CT in general (i.e. not specifically for CTCA) was available[32]. The costs occurring in the first year after a non-fatal cardiovascular event, a fatal cardiovascular event, and a non-cardiovascular fatal event were based on the EUROPA trial[70]. For subsequent years after the non-fatal event, the additional cost was estimated at £986[60]. CAD management costs for each difficult-to-image patient group were calculated using a previously published regression model, which estimates costs using patient characteristics such as age, diabetes mellitus, medication usage, and symptomatic disease[60]. Costs due to radiation-induced cancer are based on a number of previous comprehensive assessments of the economic burden of treating several different types of cancer[61].

Health related quality of life

The overall effectiveness of the three strategies was expressed in QALYs. QALYs represent a combination of life expectancy and health-related quality of life (HRQoL). The HRQoL estimates of CAD patients were based on three sources: UK population norms for the EQ5D[71], EQ5D scores per Canadian Cardiovascular Society class of angina pectoris[72] and treatment effect on HRQoL

based on the RITA2 trial[73]. These sources were used to calculate HRQoL for each difficult-to-image group[59]. It was assumed that a non-fatal event was associated with a disutility of 0.0102 for the subsequent three months[5]. Loss in QALYs due to radiation induced cancer were based on the UK population[61]. HRQoL of patients with stroke were estimated to be 0.37 using the results of the study of Sandercock et al.[30].

Assumptions

A number of assumptions were made in this study. First, the ICA ("gold standard") was assumed to have a sensitivity and specificity of 100%. Second, we assumed that all diagnostic tests are performed immediately after each other without any relevant time delay. Third, we also assumed that the sensitivity and specificity of the tests for each difficult-to-image subgroup are the same for both populations. Lastly, the complication rates of revascularization and ICA were assumed to be the same in all subgroups. The full set of assumptions is provided in Westwood et al.[32].

Analyses

Base-case scenarios were based on a probabilistic sensitivity analysis due to the non-linearity of the model. Scenario analyses were performed to determine the impact of different values for the input parameters on the ICERs. The cost of the NGCCT, the prior likelihood of CAD in the suspected population, and the complication rates were varied. The cost of NGCCT was fixed at £150 and at £207; this range was based on the bottom-up costing method where we have varied the number of procedures performed per year. The prior likelihood of the suspected population was increased to 0.3, which was the upper limit of the range when a 64-slice CT should be performed to diagnose patients suspected of CAD[10]. Worst-case and best-case scenarios for the NGCCT strategies were performed by varying the complication rates (lower and upper limits of 95% confidence interval) of a revascularization and of the test. Moreover, cost-effectiveness acceptability curves are created to present the probability of a strategy being cost-effective given the willingness-to-pay threshold. Currently, NICE applies a threshold of £20,000 to £30,000 per QALY gained[74]. More information concerning the modelling methods and input parameters can be found in Westwood et al.[32]. All analyses were performed using Microsoft Excel™ 2010.

RESULTS

The base-case results revealed that NGCCT was initially less expensive than ICA, but that the lower sensitivity and specificity of NGCCT leads to more incorrect diagnostic classifications (Table 3.1). Furthermore, the NGCCT reduces radiation induced cancer, complications (stroke & MI) and mortality due to the diagnostic procedure compared with ICA.

Table 3.1 | Intermediate outcomes

	Proportion correct classification	Misclassification		Test mortality	Test morbidity	Mortality revascularization	Morbidity revascularization[a]
		FPs	FNs				
Suspected CAD population							
ICA – only	1	–	–	0.00073	0.00064	0.00027	0.00047
NGCCT – ICA	0.9903	–	0.0097	0.00019	0.00018	0.00026	0.00044
NGCCT – only	0.8934	0.0969	0.0097	–	–	0.00039	0.00067
Known CAD population							
ICA – only	1	–	–	0.0007	0.0006	0.0030	0.0051
NGCCT – ICA	0.9818	–	0.0182	0.0001	0.0003	0.0028	0.0048
NGCCT – only	0.9042	0.0775	0.0182	–	–	0.0034	0.0058

[a] Stroke or MI due to the procedure

Suspected CAD population

Table 3.2 presents the overall costs and effects for the suspected CAD population and the cost and effects per difficult-to-image subgroup. The strategies are arranged according to increasing effectiveness and ICERs are estimated for the two most effective strategies by comparing the strategies with the strategy that is ranked lower in effectiveness.

The three strategies differed very little in their effectiveness; the ICA-only strategy was only slightly more effective than the other strategies (i.e., 10.597 QALYs vs. 10.590 QALYs for NGCCT-ICA and 10.588 for NGCCT-only). However, the ICA-only strategy was also the most expensive strategy (£6,534), followed by NGCCT-ICA (£5,950) and the NGCCT-only strategy (£5,808). The NGCCT-only strategy might be considered as a cost-effective strategy, since its effectiveness is very similar to that of the ICA-only strategy and its overall costs are lower than that of the other strategies. The ICER of NGCCT-ICA versus NGCCT-only is considerably higher (£71,000) than the currently used threshold of £20,000 to £30,000 per additional QALY. The ICA-only strategy generated the most effects but was also the most expensive strategy leading to an ICER that would exceed the threshold (£83,429). The subgroups analyses correspond with the overall results; however ICA-only is the most cost-effective strategy for patients with arrhythmias (ICER: £24,645) if a threshold of £30,000 per additional QALY is used. Figure 3.4 shows a cost-effectiveness acceptability curve; the NGCCT-only strategy has the highest probability of being cost-effective if the cost-effectiveness threshold is less than £70,000. For thresholds above £70,000, the three different strategies are more or less equivalent. However, the probability of NGCCT-only being the cost-effective strategy is still less than 50% compared with the other strategies.

Table 3.2 | Cost effectiveness of NGCCT for the suspected CAD population

Suspected CAD population	Relative proportions[a]	Costs		QALYs		ΔCosts	ΔQALYs	ICER (£/QALY)
		Mean (£)	se	Mean	se			
Overall								
NGCCT – only		5,808	573	10.588	0.109			
NGCCT – ICA		5,950	589	10.590	0.109	142	0.002	71,000
ICA – only		6,534	572	10.597	0.107	584	0.007	83,429
Obese								
NGCCT – ICA		6,297	1,237	10.508	0.167			
NGCCT – only	16.25%	6,106	1,202	10.508	0.167	–191	0.000	Dominates NGCCT – ICA
ICA – only		6,968	1,217	10.519	0.163	862	0.011	81,318
Arrhythmias								
NGCCT – ICA		6,227	1,190	9.419	0.171			
NGCCT – only	11.75%	6,077	1,161	9.42	0.171	–150	0.000	Dominates NGCCT – ICA
ICA – only		6,785	1,205	9.448	0.166	708	0.029	24,645
Heart rate >65 bpm								
NGCCT – only		6,595	1,256	10.967	0.156			
NGCCT – ICA	29.25%	6,758	1,289	10.968	0.157	162	0.001	312,047
ICA – only		7,342	1,263	10.969	0.155	584	0.001	440,057
Coronary calcium level >400								
NGCCT – only		5,962	1,168	10.201	0.169			
NGCCT – ICA	27.50%	6,142	1,248	10.202	0.169	180	0.001	205,536
ICA – only		6,801	1,189	10.21	0.167	659	0.008	80,446
Intolerance β-Blocker								
NGCCT – ICA		6,430	1,320	11.54	0.151			
ICA – only	15.25%	7,016	1,242	11.541	0.148	586	0.001	972,803
NGCCT – only		6,279	1,240	11.542	0.151	–736	0.001	Dominant

[a] Expert opinion

Known CAD population

Table 3.3 shows the cost-effectiveness results for the known CAD population. The NGCCT strategies were more effective than ICA-only in all subgroups. Overall NGCCT-only was the most effective strategy (9.538 QALYs) compared to NGCCT-ICA (9.537 QALYs) and ICA-only (9.516 QALYs). However, NGCCT-only was also more expensive (£28,228) compared with NGCCT-ICA (£27,785) leading to an ICER of £726,230 per QALY gained. Consequently, NGCCT-ICA seems to be cost-effective for the known CAD population since the ICER of NGGCT-only (£726,230) is considerably higher than the threshold of £30,000 per QALY gained. When uncertainty is taken

into account, the above results still hold. The acceptability curve graph (Figure 3.4) shows that the NGCCT-ICA strategy has the highest probability of being cost-effective independent of the willingness to pay thresholds, while the ICA-only strategy has the smallest probability of being cost-effective.

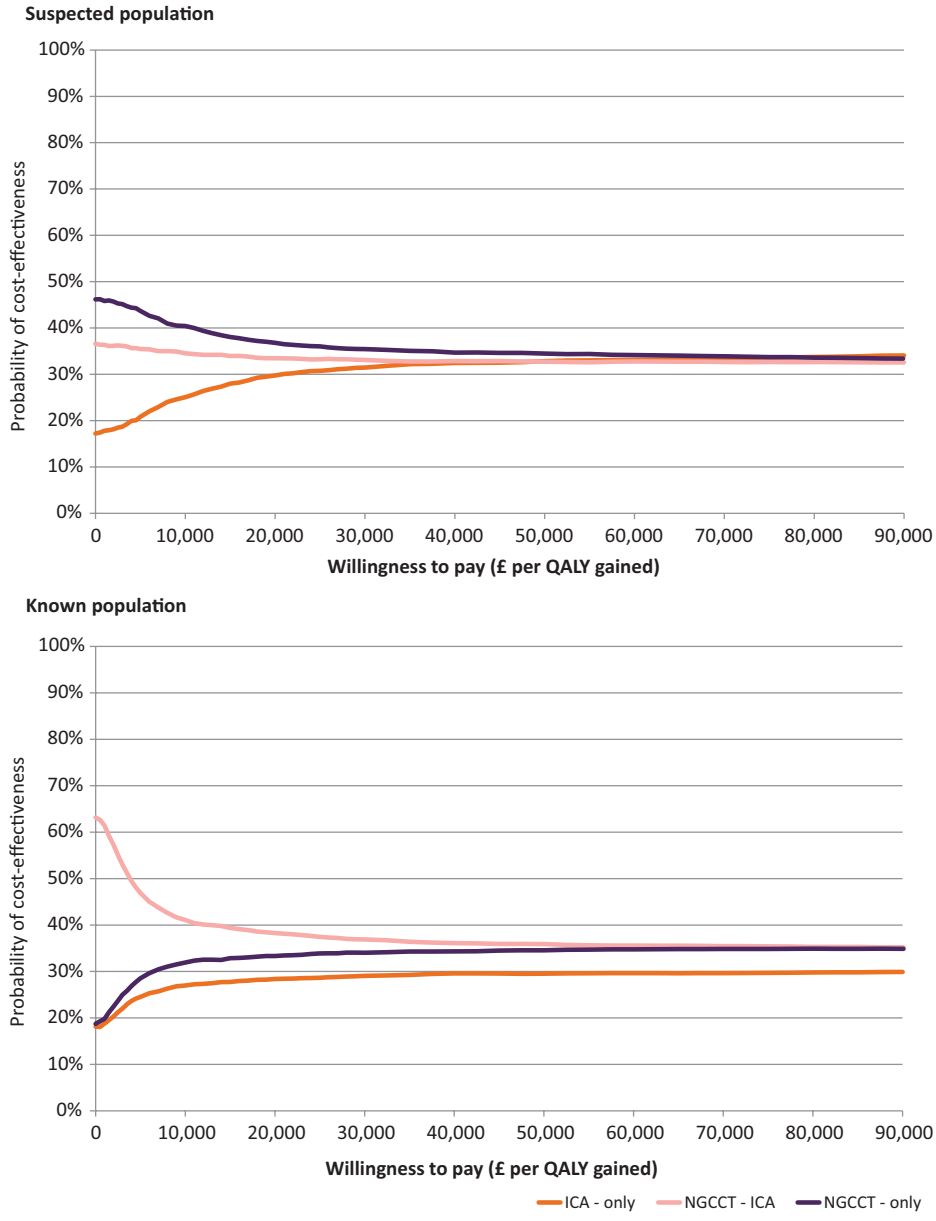

Figure 3.4 | Acceptability curves for suspected and known CAD populations

CAD: coronary artery disease; QALY: quality adjusted life years; ICA: invasive coronary angiography; NGCCT: new generation coronary computed tomography

Table 3.3 | Cost effectiveness of NGCCT for the known CAD population

Known CAD population	Relative proportions[a]	Costs		QALYs		ΔCosts	ΔQALYs	ICER (£/QALY)
		Mean (£)	se	Mean	se			
Overall								
ICA – only		28,234	502	9.516	0.288			
NGCCT – ICA		27,785	531	9.537	0.283	-449	0.022	Dominates ICA – only
NGCCT – only		28,228	498	9.538	0.286	443	0.001	726,230
Obese								
ICA – only		29,694	928	8.857	0.464			
NGCCT – only	10%	29,254	924	8.869	0.477	-439	0.012	Dominates ICA – only
NGCCT – ICA		29,177	920	8.872	0.46	-77	0.003	Dominant
Arrhythmias								
ICA – only		27,428	908	6.545	0.504			
NGCCT – ICA	7.33%	27,084	916	6.588	0.503	-344	0.043	Dominates ICA – only
NGCCT – only		27,726	971	6.595	0.499	642	0.007	90,683
Heart rate >65 bpm								
ICA – only		30,434	1,169	11.223	0.381			
NGCCT – only	27.33%	30,477	1,190	11.233	0.377	43	0.011	4,021
NGCCT – ICA		30,080	1,184	11.242	0.378	-397	0.009	Dominant
Coronary calcium level >400								
ICA – only		31,145	1,079	9.271	0.538			
NGCCT – only	25.67%	30,839	1,103	9.301	0.533	-306	0.03	Dominates ICA – only
NGCCT – ICA		30,661	1,075	9.306	0.539	-178	0.005	Dominant
Intolerance β-blockers								
ICA – only		29,339	986	10.016	0.392			
NGCCT – only	9.33%	29,354	1,004	10.039	0.392	14	0.024	610
NGCCT – ICA		28,972	988	10.042	0.394	-381	0.003	Dominant
Previous stent								
ICA – only		28,450	842	8.724	0.364			
NGCCT – ICA	11%	28,056	855	8.737	0.358	-394	0.013	Dominates ICA – only
NGCCT – only		28,672	888	8.744	0.354	617	0.007	93,526
Previous CABG								
ICA – only		28,466	844	8.719	0.363			
NGCCT – ICA	9.33%	28,088	859	8.725	0.36	-378	0.006	Dominates ICA – only
NGCCT – only		28,554	1,028	8.725	0.359	466	0	2,943,850

[a] Expert opinion

Scenario analyses

The scenario analysis with a cost price of £150 for the NGCCT did not affect the overall results; the NGCCT-ICA strategy was still the most favourable strategy. However, when the price of the NGCCT was increased to £207, the ICA-only strategy became less expensive than the NGCCT-only strategy for the known CAD population. Varying the complication rates and the prior likelihood of having CAD for the suspected population did not change the overall results.

DISCUSSION

64-slice CT has proven accuracy for the diagnosis of CAD in most patients[55-57]. However, these scanners are less useful for difficult-to-image patient groups, e.g. those with irregular or fast heartbeats, those who are obese, or in whom artefacts produced by high levels of coronary calcium or existing stents might reduce image quality. Newer generation CT scanners have the advantage of being capable of producing diagnostic quality images in these patient groups. This study has estimated the cost-effectiveness of new generation CT scanners in these difficult-to-image patients.

For patients with suspected CAD, the NGCCT-only strategy might be considered as cost-effective, since its effectiveness is very similar to that of the most effective strategy (difference: -0.009 QALYs) and since its overall costs are much lower than those of the other strategies. For patients with known CAD, a cost-effective strategy is probably NGCCT followed by ICA if the NGCCT is positive (NGCCT-ICA), since it yields the highest cost-saving, and dominates the ICA-only strategy.

Implications

The NICE recommendations about the use of these scanners in the UK were based in part on the results of this study. They recommended the use of new generation cardiac CT scanners as an option for first line imaging of the coronary arteries in patients with suspected CAD and for first-line evaluation of disease progression to establish the need for revascularization in patients with known CAD in whom imaging with earlier generation CT scanners is difficult[75].

Strengths and limitations

The strength of this cost-effectiveness analysis is that we were able to capture as well as possible the whole range of patient experience from diagnostics to clinical pathway to complications and radiation by combining economic model components. Of course, combining evidence with the use of economic models could be viewed as a limitation because it introduces uncertainty and it was necessary to make several assumptions. However, assumptions and evidence sources have been explicitly reported and uncertainty accounted for by probabilistic sensitivity analyses and scenario analyses.

The estimated accuracy of the NGCCT is based on the accuracy of ICA, which was assumed to be 100%. However, the use of ICA as the gold standard is very common in this field[55] but this may have influenced our results since the estimated accuracy of the NGCCT is also based on the accuracy of the ICA. In addition, ICA in combination with fractional flow reserve is currently a frequently used procedure and can be considered as a better alternative than ICA-only[76]. Moreover, accuracy estimates for NGCCT were only based on studies evaluating Somatom definition Flash, Discovery CT750 HD and Aquilion ONE since none of the studies evaluating the Brilliance iCT were eligible for inclusion. Extrapolation of the cost-effectiveness results to the other NGCCTs is therefore debatable. Furthermore, the accuracy estimates of the NGCCT are assumed to be the same for the known and suspected population and do not differ between the different types of NGCCT scanners. It is uncertain whether these assumptions may have led to an overestimate or an underestimate of the cost-effectiveness of NGCCT-only and NGCCT-ICA strategies.

The prior likelihood of CAD in the suspected CAD population was based on the clinical guideline for chest pain of recent onset[10] and for the known population it was based on the prior likelihood estimated by the CE-MARC study[59]. For the suspected CAD group, we had to rely on the recommendations of the clinical guideline "Chest pain of recent onset"[10] to quantify the prior likelihood. According to the clinical guideline, CT scans are recommended for use in the diagnostic path of patients with a prior likelihood of CAD of 10–29% and a non-zero calcium score [10]. This likelihood is based on presence of certain clinical symptoms (suggestive of angina), age, gender, diabetes, smoking and hyperlipidaemia. However, scenario analyses showed that the overall results did not change when the prior probability of patients suspected of CAD increased. For the prior likelihood estimate in the known CAD population, it is not entirely certain that the CE-MARC study[59] and our study consider exactly the same patient population. It is therefore possible that the actual prior likelihood in our populations differs from that currently assumed in our model.

Complication rates for the initial procedures are a compilation of various sources and are assumed to be the same for all subgroups. This assumption may have led to an inaccurate estimation of the MI and stroke rates for CABG, PCI and ICA. Potential differences in any of these factors could lead to different conclusions for the various NGCCTs. However, we have performed scenario analyses changing the parameters, which did not alter our conclusions.

Generalizability

The results of this analysis may differ by setting due to differences in costs, incidence and severity of the CAD, the availability of health care resources and clinical practice patterns[77]. However, the modelling methods and input parameters are presented in a transparent and reproducible way and therefore the developed model can be adapted to other jurisdictions.

Conclusions

The use of NGCCT in difficult-to-image CAD patients might be considered cost-effective based on the cost-effectiveness thresholds used in England and Wales. NGCCT is equal in effectiveness to ICA but is cost-saving in both the suspected CAD and the known CAD populations. NGCCT is therefore recommended in the assessment of patients who are difficult to image with earlier CT scanners.

Table S3.1 | Input parameters and costs

	Value	Source
Prevalence		
Suspected CAD population	0.200 (0.1 – 0.29)	[10]
Known CAD population	0.395	[59]
Accuracy estimates		
Sensitivity		
ICA: 'gold' standard	1	Assumption [55]
NGCCT	0.904 – 0.977[a]	[78]
Specificity		
ICA: 'gold' standard	1	Assumption [55]
NGCCT	0.816 – 0.921[a]	[78]
Complications ICA		
Mortality rate	0.0007	[63]
Cerebrovascular accident rate	0.0006	[63]
Myocardial infarction rate	0.00003	[63]
Complications PCI		
Mortality rate	0.0029	[66]
Cerebrovascular accident rate	0.0005	[66]
Myocardial infarction rate	0.0005	[66]
Complications CABG		
Mortality rate	0.018	[67]
Cerebrovascular accident rate	0.016	[64]
Myocardial infarction rate	0.024	[64,65]
Costs per procedure		
ICA	1,003	[79]
NGCCT	169	[78]
Coronary artery bypass graft	8,280	[79]
Percutaneous coronary intervention	3,633	[79]
Coronary artery bypass graft + ICA	9,242	[79]
Percutaneous coronary intervention + ICA	4,196	[79]

Table S3.1 | *(Continued)*

	Value	Source
Cost per event		
Non-fatal event (MI or cardiac arrest)	11,805	60
Cardiovascular fatal event	3,641	60
Non-cardiovascular fatal event	1,241	60
Non-fatal event history	986[b]	60
Background costs	regression[c]	60
Stroke first year	9,429[b]	80
Stroke subsequent years	4,894[b]	80
Radiation induced cancer	12,389 – 22,712[d]	61

[a] Range for all subgroups; [b] Per cycle; [c] Depending on age, the existence of cardiovascular diseases, diabetes mellitus, medication usage, clearance and symptomatic disease; [d] Depending on type of cancer

Challenges
Devices
Tests
Modelling
Cardiovascular
Technologies
QALY
ICER
Analyses
Data
Blood
Results
Markov
Cost-effectiveness
Disease
Costs
CVD
CAD
PCI
Thesis
Extrapolating
Diagnosis
Prevention
Intervention
Specificity
Sensitivity Analyses
Scenario Analyses
Drugs
Risks
Follow-up
Structure
Guidelines
Angina
EVAR
RCT
TAVI
Validity
Bias
Stroke
Literature
Precision
Efficacy
Identification
Persistence
Learning Curve
Decision Tree
Frequency
Importance
Accuracy
CT-scanner
Synergy
Gold Standard
False Negative
False Positive
True Negative
Regression
Outcomes
Survival
Perspective
Methods
Budget
Interaction
Statistics
Monitoring
Indication
Transition
ICA
Prior Likelihood
Real-world
Care Pathway
Prevalence
Systolic
Diastolic
Ischemic
Technologies
Observational
Review
Probabilities
Short Term
Utilities
Recommendations
Plaque
Statin
Document Analysis
Artery
Fevar
AAA
QoL
CABG
Bevar
Surgical
Heart
Wait Time
Treatment
Thrombosis
Comparators
Prognostic
Abdomen
Disorders
Effectiveness
Impact
Bypass
Compliance
Relative Risk
Limitations
Hospital
Angiography
Disease Management
Heterogeneity
Cerebrovascular
Balloon

Chapter 4

Treatment variation in patients with stable or unstable coronary artery disease

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ABSTRACT

Aim: Variations in treatment are the result of differences in demographic and clinical factors (e.g. anatomy) but physician and hospital factors may also contribute to treatment variation. The choice of treatment is considered important since it could lead to differences in long-term outcomes. This study explores the associations with stent choice; i.e. drug-eluting stent (DES) versus bare metal stents (BMS) for Dutch patients diagnosed with stable or unstable coronary artery disease (CAD).

Methods and results: Associations with treatment decisions were based on a prospective cohort of 692 patients with unstable or stable CAD. Of those patients 442 patients were treated with BMS or DES. Multiple logistic regression analyses were performed to identify variables associated with stent choice. Bivariate analyses showed that NYHA class, number of diseased vessels, previous PCI, smoking, diabetes, and the treating hospital were associated with stent type. After correcting for other associations the treating hospital remained significantly associated with stent type in the stable CAD population.

Conclusions: This study showed that several factors were associated with stent choice. While, patients generally appear to receive the most optimal stent given their clinical characteristics, stent choice seems partially determined by the treating hospital, which may lead to differences in long-term outcomes.

INTRODUCTION

Despite improvement in the prognosis of patients with cardiovascular disease (CVD) it still remains the second leading cause of death across the Western world and one of the major causes of disability[1]. For many years patients with coronary artery disease (CAD), the most frequent type of CVD, have been treated mainly with a percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or with medication only. Both revascularizations reduce the incidence of death and myocardial infarction (MI) in CAD patients compared with no treatment, but most patients are now treated with a PCI. In 2012 approximately 39,000 PCIs were performed in the Netherlands[81]. Originally, a PCI was performed with an expanding balloon to dilate the narrowed segment of the artery but in 1994 the bare-metal stent (BMS) was developed to prevent restenosis[11]. However, the restenosis rate leading to repeat revascularizations of the target lesion was still substantially high after the introduction of BMS. In 2003, the drug-eluting stent (DES) was approved to the market to reduce restenosis compared with BMS (8.4% versus 20.9%)[12]. However, patients treated with DES, especially the early-generation, might have a higher chance of developing very late stent thrombosis (0.7% versus 0.1%)[12]. Both types of stents have pros and cons; decisions should be based on what is considered appropriate for a patient since the choice of stent type may have impact on long-term outcomes. Variations in treatment are the result of differences in patient characteristics and clinical factors (e.g. anatomy) but previous studies have shown that the physician and hospital factors may contribute to treatment variation. In the UK, stent choice was associated with the operator and the treating hospital[82]. Tu et al.[83] have shown that the physician performing the diagnostic catheterization and the treating hospital were strong independent predictors of the type of revascularization (CABG versus PCI) in Canada. Furthermore, the type of stent was also determined by the type of payer (e.g. Medicaid, private insurance)[84]. Of course these results may be expected to be health care system specific and do not apply for Dutch patients, since the Netherlands have a centrally publicly funded healthcare system.

This study will explore the associations with stent choice (DES or BMS) for Dutch patients diagnosed with stable CAD or unstable CAD focusing on variation due to clinical factors and treating hospital.

METHODS

Study design

Treatment variation of patients with stable or unstable CAD was explored through analysing data from the Circulating Cells prospective cohort study, which has the aim of discovering markers that identify patients who are at an increased risk of developing a cardiovascular event. In

this multicentre study, patients undergoing a coronary angiography were included if they had known or suspected stable or unstable CAD; specific diagnoses included unstable angina and non-ST elevation MI (NSTEMI). Patients with relevant concomitant disease, relevant recent infectious disease (in the last 6 weeks) or suspected elevated state of the immune system were excluded. More details about the Circulating Cells cohort study design can be found in a previous publication[85].

Treatment

Patients undergoing a coronary angiography were asked to participate in the study. Data were collected regarding patient characteristics, test results and treatment decisions. Patients who were treated with a PCI could have received a BMS, DES, drug-eluting balloon angioplasty or standard balloon angioplasty. The aim of this study is to examine the factors that are associated with stent choice (DES vs. BMS), meaning that patients treated solely with drug-eluting balloon angioplasty or standard balloon angioplasty are excluded from the analyses. Stent choice DES was defined as a PCI with at least one DES, including patients treated with only DES but also patients treated with DES in combination with BMS, drug-eluting balloon angioplasty or standard balloon angioplasty. Stent choice BMS was defined as a PCI with only BMS such that patients treated with BMS in combination with balloon angioplasty or DES are excluded.

Data and statistical analyses

Choice of stent type (DES or BMS) was compared between patient subgroups (determined by diagnosis). The following baseline characteristics were also collected during the study: age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), thrombolysis in myocardial infarction (TIMI) score for unstable CAD patients, New York Heart Association (NYHA) class, number of diseased vessels (50–99% stenosis), cardiac history (previous heart failure, previous MI, previous PCI, and previous CABG), non-cardiac history (cerebrovascular accident (CVA) or transient ischaemic attack (TIA), pulmonary disease, peripheral vessel disease (PVD), and renal failure), and CVD risk factors (diabetes mellitus, hypertension, hyperlipidaemia, smoking, and pack-years (tobacco)).

Multiple imputation was used to prevent patients from being excluded from the analyses due to missing values. Baseline characteristics (SBP, DBP, BMI, NYHA class, previous heart failure, previous MI, CVA or TIA, pulmonary disease, PVD, renal failure, diabetes mellitus, hypertension, hyperlipidaemia, current smoker and pack years) were missing for less than 2% of all cases except pack years, which was missing for 14% of all cases. These characteristics were imputed using predictive mean matching for scale variables. Five imputation sets were created with ten iterations each using fully conditional specification in SPSS 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Age, gender, previous PCI, previous CABG, and diagnosis were only used as predictors and not imputed since there were no missing values for these variables.

Differences between groups were tested using Chi-squared analysis for categorical variables. Bivariate analyses using logistic regression were performed to identify variables that were associated with choice for stent type; stable and unstable CAD patients were analysed separately. Backwards selection was used to create the final multivariate model(s). P values lower than 0.05 were considered statistically significant, although a higher threshold of 0.1 was used to select variables for the multivariate analysis. Associations were discussed with clinical experts in order to see if the results make sense (face validity).

Table 4.1 | Baseline characteristics

	All patients after imputation			Patients with stable CAD			Patients with unstable CAD			
	mean	sd	N[b]	mean	sd	N[b]	mean	sd	N[b]	p value[a]
Baseline characteristics										
Age	62.72	10	442	62.96	10	358	61.71	11	84	0.319
Male (%)	72%		442	73%		358	68%		84	0.354
SBP (mmHg)	135	19	442	135	19	358	134	21	84	0.748
DBP (mmHg)	77	11	442	77	11	358	79	11	84	0.273
BMI (kg/m^2)	28	4	442	28	4	358	27	4	84	0.266
TIMI score[c]										
1	8%		83				8%		83	
2	18%		83				18%		83	
3	30%		83				30%		83	
4	28%		83				28%		83	
5	12%		83				12%		83	
6+7	4%		83				4%		83	
Number of diseased vessels (50–99%)										0.077
1	44%		442	46%		358	36%		84	
>1	56%		442	54%		358	64%		84	
NYHA										**p<0.001**
NYHA I	73%		442	73%		358	76%		84	
NYHA II	18%		442	20%		358	7%		84	
NYHA III	6%		442	7%		358	4%		84	
NYHA IV	2%		442	0%		358	13%		84	
Cardiac history (%)										
Previous heart failure	2%		442	2%		358	1%		84	0.542
Previous MI	31%		442	33%		358	23%		84	0.066
Previous PTCA	33%		442	35%		358	26%		84	0.116
Previous CABG	7%		442	8%		358	5%		84	0.369

Table 4.1 | *(Continued)*

	All patients after imputation			Patients with stable CAD			Patients with unstable CAD			
	mean	sd	N[b]	mean	sd	N[b]	mean	sd	N[b]	p value[a]
Non-cardiac history (%)										
CVA/TIA	8%		442	6%		358	14%		84	**0.017**
Pulmonary disease	11%		442	10%		358	14%		84	0.242
Peripheral vessel disease	13%		442	13%		358	14%		84	0.684
Renal failure	3%		442	4%		358	1%		84	0.25
Risk factors (%)										
Diabetes mellitus	21%		442	22%		358	20%		84	0.764
Hypertension	66%		442	67%		358	60%		84	0.189
Hyperlipidemia	68%		442	70%		358	60%		84	0.057
Current smokers (%)	19%		442	16%		358	32%		84	**0.001**
Pack years[d]	19.7	18	442	19.2	18.1	358	21.9	22	84	0.302
Diagnosis (%)										
Stable angina	81%		442							
Unstable angina	10%		442							
NSTEMI	9%		442							
Treatment / stent choice										0.736
DES	66%		442	66%		358	68%		84	
BMS	34%		442	34%		358	32%		84	
Hospital										
I	29%		442	28%		358	37%		84	
II	22%		442	24%		358	13%		84	
III	18%		442	14%		358	37%		84	
IV	30%		442	34%		358	13%		84	

[a] Stable versus unstable; [b] Number of patients on which the analyses were based; [c] only reported for unstable angina and NSTEMI; [d] Number of packs per day multiplied with years of smoking

BMI: body mass index; CABG: coronary artery bypass graft; CVA: cerebrovascular accident; DBP: diastolic blood pressure; MI: myocardial infarction; NA: not applicable; NSTEMI: non ST elevation myocardial infarction; NYHA: New York heart association; PTCA: percutaneous transluminal coronary angioplasty; SBP: systolic blood pressure; TIA: transient ischaemic attack; TIMI: thrombolysis in myocardial infarction

RESULTS

In total, 714 patients were included in the Circulating Cells cohort, 22 of whom were excluded from the analyses since they did not have significant coronary atherosclerosis. The remaining 692 patients were included in three teaching hospitals and one general hospital and 477 patients were treated with a PCI. Of those patients, 442 patients were treated with BMS or DES. Others were treated with a combination of a BMS and balloon angioplasty (N=4), drug-eluting balloon

angioplasty or standard balloon angioplasty (N=18) or missing (N=13) and are excluded from the analysis. The number of patients treated per hospital (I-IV) was 130, 98, 81, and 133, respectively. Table 4.1 presents the baseline demographic and angiographic characteristics of the included patients. The mean age of the cohort was 63 years and 72% were male. The majority (81%) of the patients were diagnosed with stable CAD (including silent ischemia) after the coronary angiography. There were three significant differences in characteristics of stable CAD (N=358) and unstable CAD patients (N=84). Stable CAD patients more often had a lower NYHA class, were less often current smokers and had less often experienced a CVA/TIA compared to unstable CAD patients.

In total 771 stents were used to treat 442 patients with 612 target lesions. On average 1.385 target lesions were stented per patient (range 1–3), where 1.260 stents were used per lesion and 1.744 stents (range 1–6) per patient were used. Of the 442 patients, 66% was treated with one or more drug-eluting stents. Bivariate analyses (Table 4.2) showed that NYHA class, number of diseased vessels, previous PCI, smoking, diabetes and the treating hospital were significantly associated with stent choice for a patient. The frequency of DES use varied widely (50–99%) between the four hospitals, considering the total population. The variation in stent choice was larger in the unstable patient group (45–100%).

Table 4.2 | Associations with therapeutic decision (DES vs BMS)

	All patients			Patients with stable CAD			Patients with unstable CAD		
	DES (%) / OR	**N**	**p value**	**DES (%) / OR**	**N**	**p value**	**DES (%) / OR**	**N**	**p value**
Overall	66%	442		66%	358		68%	84	
Diagnosis			0.558						
Stable CAD	66%	358							
Unstable angina	63%	46							
NSTEMI	74%	38							
Hospital			**p<0.001**			**p<0.001**			**p<0.001**
1	50%	130		52%	99		45%	31	
2	64%	98		66%	87		55%	11	
3	99%	81		98%	50		100%	31	
4	64%	133		65%	122		55%	11	
Baseline characteristics									
Age (years)	1.008	442	0.387	1.005	358	0.682	1.023	84	0.272
Gender			0.474			0.46			0.872
Male	67%	318		67%	261		68%	57	
Female	64%	124		63%	97		67%	27	

Table 4.2 | *(Continued)*

	All patients			Patients with stable CAD			Patients with unstable CAD		
	DES (%) / OR	N	p value	DES (%) / OR	N	p value	DES (%) / OR	N	p value
SBP (mmHg)	1.007	442	0.188	1.003	358	0.598	1.022	84	0.074
DBP (mmHg)	0.998	442	0.815	0.997	358	0.767	1.001	84	0.968
BMI (kg/m2)	1.038	442	0.128	1.049	358	0.08	0.994	84	0.912
TIMI score[a]			0.085						0.085
1	71%	7					71%	7	
2	80%	15					80%	15	
3	48%	25					48%	25	
4	83%	23					83%	23	
5	60%	10					60%	10	
6+7	100%	3					100%	3	
NYHA			**p<0.01**			**0.036**			**0.011**
NYHA I	62%	324		63%	260		59%	64	
NYHA II	71%	79		69%	73		100%	6	
NYHA III & IV	90%	39		88%	25		93%	14	
Number of diseased vessels			**p<0.01**			**p<0.01**			0.102
1	58%	196		58%	166		57%	30	
>1	73%	246		72%	192		74%	54	
Cardiac history									
Previous heart failure			0.981			0.836			0.489
yes	67%	9		63%	8		100%	1	
no	66%	433		66%	350		67%	83	
Previous MI			0.077			0.090			0.536
yes	72%	137		72%	118		74%	19	
no	64%	305		63%	240		66%	65	
Previous PTCA			**p<0.01**			**p<0.01**			0.271
yes	76%	148		76%	126		77%	22	
no	61%	294		60%	232		65%	62	
Previous CABG			0.541			0.736			0.433
yes	61%	31		63%	27		50%	4	
no	67%	411		66%	331		69%	80	
Non-cardiac history									
CVA/TIA			0.748			0.682			0.924
yes	69%	35		70%	23		67%	12	
no	66%	407		66%	335		68%	72	

Table 4.2 | *(Continued)*

	All patients			Patients with stable CAD			Patients with unstable CAD		
	DES (%) / OR	N	p value	DES (%) / OR	N	p value	DES (%) / OR	N	p value
Pulmonary disease			0.103			0.142			0.445
yes	56%	47		55%	35		58%	12	
no	68%	395		36%	323		69%	72	
PVD			0.086			0.124			0.445
yes	56%	57		56%	45		58%	12	
no	68%	385		67%	313		69%	72	
Renal failure			0.059			0.126			0.144
yes	43%	14		46%	13		0%	1	
no	67%	428		67%	345		69%	83	
Risk factors									
Diabetes mellitus			**p<0.001**			**p<0.001**			**0.009**
yes	93%	95		92%	78		94%	17	
no	59%	347		59%	280		61%	67	
Hypertension			0.306			0.498			0.324
yes	68%	290		67%	240		72%	50	
no	63%	152		63%	118		62%	34	
Hyperlipidaemia			0.943			0.427			0.144
yes	66%	302		65%	252		74%	50	
no	67%	140		69%	106		59%	34	
Current smokers			**0.037**			0.066			0.246
yes	57%	85		55%	58		59%	27	
no	69%	357		68%	300		72%	57	
Pack years[b]	1.001	442	0.898	1.000	358	0.974	1.002	84	0.877

[a] only for unstable angina and NSTEMI; [b] Number of packs per day multiplied with years of smoking
BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CVA: cerebrovascular accident; DBP: diastolic blood pressure; MI: myocardial infarction; NA: not applicable; NSTEMI: non ST elevation myocardial infarction; NYHA: New York heart association; PTCA: percutaneous transluminal coronary angioplasty; PVD: peripheral vessel disease; SBP: systolic blood pressure; TIA: transient ischaemic attack; TIM: thrombolysis in myocardial infarction

All multivariate analyses (Table 4.3) showed that patients with diabetes had a significantly higher chance of receiving DES. The use of DES versus BMS in the stable CAD population was not only associated with diabetes but also with the treating hospital, smoking status, and previous PCI. Patients treated in hospital II or III, patients having diabetes, and patients with a previous PCI had a higher chance of being treated with DES. Patients treated in hospital I and patients who were current smokers had a lower chance of being treated with DES.

Table 4.3 | Multivariate analyses therapeutic decision (BMS versus DES)

Total population (N=442)	**Bivariate analyses (OR)**	**Multivariate analyses (OR)**	**p value***
Number of diseased vessels			
1	0.520	0.560	0.006
>1	ref		
NYHA class			
NYHA class I	ref		
NYHA class II	1.478		
NYHA class III + IV	5.311		
Hospital			
1	0.565		
2	1.016		
3	45.176		
4	ref		
Diabetes (yes vs no)	8.680	8.318	p<0.001
Renal artery disease (yes vs no)	0.368		
Current smoker (yes vs no)	0.599		
Previous MI (yes vs no)	1.486		
PVD (yes vs no)	1.017		
Previous PTCA (yes vs no)	2.045		
TIMI score[a]			
1	ref		
2	1.20		
3	0.37		
4	2.000		
5	0.600		
6+7	646189937		
Constant		1.911	p<0.001
Nagelkerke R^2		16%	
Stable CAD (N=358)			
BMI (kg/m²)	1.049		
Hospital			
1	0.578	0.466	0.013
2	1.034	1.047	0.884
3	26.671	29.381	0.001
4	ref	ref	
Previous MI (yes vs no)	1.513		

Table 4.3 | *(Continued)*

	Bivariate analyses (OR)	Multivariate analyses (OR)	p value*
NYHA class			
NYHA class I	ref		
NYHA class II	1.280		
NYHA class III + IV	4.319		
Number of diseased vessels			
1	0.536		
>1	ref		
Current smoker (yes vs no)	0.588	0.404	0.014
Diabetes (yes vs no)	8.454	12.001	p<0.001
Previous PTCA (yes vs no)	2.103	2.284	0.003
Constant		1.207	0.397
Nagelkerke R^2		33%	
Unstable CAD (N=84)			
Hospital			
1	0.686		
2	1.000		
3	1346229036		
4	ref		
NYHA class			
NYHA class I	ref		
NYHA class II	1105324892		
NYHA class III + IV	8.895		
Diabetes (yes vs no)	10.146	10.146	0.029
TIMI score[a]			
1	ref		
2	1.600		
3	0.369		
4	1.900		
5	0.600		
6+7	646189937		
SBP (mmHg)	1.007		
Constant		1.577	0.069
Nagelkerke R^2		13%	

[a] P value of multivariate analyses

SBP: systolic blood pressure; BMI: body mass index; NYHA: New York heart association; PTCA: percutaneous transluminal coronary angioplasty; TIMI: Thrombolysis In Myocardial Infarction

DISCUSSION

This study explored the factors associated with stent choice for Dutch patients diagnosed with stable CAD or unstable CAD. Various factors are associated with the frequency of DES use, including diabetes, previous PCI, number of diseased vessels, NYHA class, smoking and the hospital where patients were treated.

Patients requiring a PCI were in most cases treated with at least one DES (66%), which is in line with the guidelines that suggest that patients with stable CAD should receive a DES if there is no contraindication of prolonged dual antiplatelet therapy[86]. Furthermore, DES is recommended over BMS in NSTEMI or unstable angina patients with diabetes[87]. Since patients with diabetes have a higher restenosis risk than patients without diabetes, DES is considered the most optimal treatment for these patients since DES reduces restenosis compared with BMS. Consequently, diabetes was significantly associated with stent choice in this study. Patients who have been treated before with a PCI were also more likely to receive DES (76%); these patients have a higher risk of developing restenosis and thus DES was preferred. Patients with multi-vessel disease (73% DES) and patients with a high NYHA class (range I-IV: 62–90% DES) were significantly more frequently treated with DES. Studies suggest that patients with multi-vessel disease should be treated with a CABG or a PCI using DES since these interventions have shown to be more effective than BMS[88]. Patients currently smoking were less often treated with DES.

These clinical factors can be considered as legitimate leading to variation in stent choice. However, 19% of the variation in stent choice was explained for by these factors in the stable CAD population. Beside clinical factors other potential reasons for treatment variation could exist due to: 1) the operator, 2) the availability and supply of resources, or 3) the preferences of the patient. Considering operator variation, physicians use different methods to decide which stent is most suited for a particular patient. It is known that some physicians are believers of DES and some do not believe in the added value of DES compared with BMS, while BMS is less expensive. It is likely that believers use DES more often than physicians who can be considered as non-believers. DES has shown in several randomized clinical trials to be more effective than BMS for several indications (e.g. diabetes, long lesions). Some operators strictly follow the results of these trials and the guidelines while some operators use DES also for other indications with a high restenosis risk since guidelines do not provide recommendations concerning the most optimal stent for every type of patient, although it is probably unrealistic to expect this. In our study, one hospital treated almost all patients with DES (99%); probably DES was used also for “off-label” indications. A Dutch report concluded that world-wide in 47–81% of the patients DES is used off-label leading to differences in safety and clinical effectiveness[89]. The second potential reason, availability and supply of resources, focuses on the hospital level. In our analyses, the treating hospital was significantly associated with stent choice even after correcting for clinical factors in the stable

CAD group. After adding treating hospital to the regression analysis with only clinical factors, 33% of the variation in stent choice could be explained instead of 19%. The analyses showed that the frequency of DES use ranged from 50–99% of all patients across hospitals. This difference could result from a difference in patient case mix, despite the adjustment for many individual patient characteristics in the analyses. Furthermore, payment arrangements with stent manufacturers and budget constraints may have influenced the stent choice. Another potential reason, patient preference, could have influenced the variation in stent choice. However, we expect this to be minimal since both interventions can be considered as equally invasive.

Implications

In general, patients receive the most optimal stent given their clinical characteristics. However, stent choice is also determined by the treating hospital probably due to operator variation and availability and supply of resources. Variation should only occur due to demographic and angiographic factors. When variation is due to factors other than demographic or angiographic it could lead to less optimal stent choices and subsequently differences in long term outcomes.

Patients receiving DES have a lower risk of target lesion revascularization than patients treated with BMS[12]. However, there is some concern of late stent thrombosis that may occur more frequently after DES than BMS[12]. Besides the implications of treatment variation on the effectiveness, it is also important to consider the implications of treatment variation on the costs. While BMS is a less expensive stent than DES, BMS leads to more reinterventions than DES. Several economic evaluations have estimated the cost-effectiveness of DES versus BMS and many of the studies concluded that initial DES treatment was overall more expensive than the BMS-strategy[90-101]; the reduction in reinterventions did not offset the initial higher stent costs. In most of the studies DES was slightly more effective[90-101] leading often to an incremental cost-effectiveness ratio that could not be considered cost-effective[91,92,95,96,101]. However, some specific subgroups (patients with diabetes, patients with complex lesions (i.e. restenotic, angulation <45°, calcified or long), patients with complex vessels (i.e. small), patients with multi-vessel disease, and patients with a combination of these risk factors), were identified in which DES resulted in a higher health gain in terms of quality-adjusted life-years compared to subgroups who were not at high risk of restenosis and complications. Consequently, in these subgroups, DES was considered more cost-effective. In our study some of these specific subgroups were also associated with a more frequent use of DES.

Limitations

The factors examined in the analyses explained 13–33% of the variation in treatment decisions, depending on the specific subpopulation. While the treating hospital was associated with stent choice, it is possible that hospital is a proxy for a pre-existing patient case mix. Many clinical factors were included in the regression models but it is possible that factors that are of predictive

value were not included. Furthermore, the underlying reason why the treating hospital is associated with stent choice is not clear. This could be due to the operator (e.g. experience), of which data were not available for our analyses, or the availability and supply of resources might explain why the treating hospital is associated, even though the Netherlands has a centrally publicly funded healthcare system.

Most of the patients (81%) in this study had stable CAD, so only a relatively small number of patients (N=84) had unstable CAD. This may have limited the power to identify existing associations between stent choice and patient characteristics and may explain why only a few characteristics were significantly associated.

We were not able to compare patients treated solely with BMS and patients treated solely with DES. Stent choice DES was defined as a PCI with at least one DES which includes patients treated with only DES but also patients treated with DES in combination with BMS, drug-eluting balloon angioplasty or standard balloon angioplasty. Consequently, the associations that we have found actually explain why some patients receive DES and why other patients did not receive DES.

In addition, this study did not take into consideration the differences within stent choice. For example, ultra-thin struts BMS lead to less restenosis than thicker struts BMS. In the SOLSTICE registry it was shown that ultra-thin strut BMS leads to encouraging 6 months major adverse cardiac event rates (5.8%), including target lesion revascularizations[102]. Furthermore, we did not made a distinction between the several types of drugs (e.g. paclitaxel, sirolimus or everolimus) that are used for DES which may also have an effect on clinical outcomes.

Lastly, the latest guideline on myocardial revascularization[103] concluded that the newer generation DES have improved safety outcomes including death, MI and stent thrombosis compared with early-generation DES and BMS. During this study, this guideline was not available and thus it is possible that stent choice might be somewhat different if the new guidelines were applicable; DES could be more frequently used. Furthermore, we did not focus on fully bioresorbable stents which has promising clinical outcomes since it provides desirable transient vessel support without compromising the restoration of normal vessel biology, vessel imaging or treatment options in the long run[104]. Consequently, the stent evaluated in the Circulating cells cohort may not reflect the stent choices that will be made in the near future.

Recommendations

This study showed the existence of treatment variation across hospitals that may have an impact on long-term outcomes. It would be interesting to investigate if the treatment variation seen in this cohort will actually lead to difference in long-term outcomes and costs, which could be

achieved by increasing the follow-up period. Van der Sijde et al.[105] have also emphasized the role of clinical observations to determine the most appropriate indication for specific types of stents.

Conclusions

This study showed that several clinical factors were associated with stent choice (DES or BMS) for CAD treatment, including diabetes, smoking, NYHA class, multi-vessel disease and previous PCI. In general, it appears that patients receive the most optimal stent given their clinical characteristics. After correcting for the clinical factors, stent choice was also associated with the treating hospital probably due to operator variation and the availability and supply of specific stent types. These differences may lead differences in long term outcomes.


Challenges
Modelling
Cardiovascular
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ICER
Analyses
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Data
Blood
Results
Markov
Extrapolating
Costs
CVD
Thesis
PCI
CAD
Drugs
Risks
Angina
Intervention
Follow-up
Diagnosis
Prevention
Structure
Precision
Validity
Bias
Sensitivity Analyses
Scenario Analyses
Specificity
Guidelines
EVAR
RCT
TAVI
Short Term
Survival
Decision Tree
Frequency
Stroke
Literature
Efficacy
Persistence
Identification
Learning Curve
Gold Standard
False Negative
True Negative
Care Pathway
Prevalence
Real-world
Observational
Review
Technologies
QoL
CT-scanner
Synergy
Importance
Management
Interaction
Statistics
Monitoring
Indication
Limitations
Transition
Relative Risk
Compliance

Chapter 5

Health related quality of life in patients with stable or unstable coronary artery disease and its associations with patient characteristics

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ABSTRACT

Introduction: Patients with coronary artery disease (CAD) are known to have a reduced health-related quality of life (HRQoL) compared with the general population. Poor HRQoL also seems to be associated with long-term morbidity and mortality. Therefore, insight into the patient characteristics which are associated with poor HRQoL may help to identify ways in which patient care can be improved.

Methods: 465 patients had filled in at least one question of the SF-36 questionnaire which was used to estimate HRQoL (SF-6D), physical (PCS) and mental (MCS) component scores. Multiple imputation of missing values resulted in a population of 441 patients. Multiple linear regression analysis was performed to identify variables that were associated with HRQoL and component scores.

Results: The average SF-6D index of all patients was 0.671±0.134. Multivariate analyses showed significant associations with gender, systolic blood pressure, BMI, previous percutaneous coronary intervention, New York Heart Association class, previous cerebrovascular accident or transient ischaemic attack, peripheral vascular disease, pack-years (tobacco) and pulmonary disease in the stable CAD group. Unstable CAD patients had higher average PCS, MCS and SF-36 dimension scores than stable CAD patients. The mental health dimension was the least affected dimension of the SF-36 but CAD had a negative impact on the physical dimensions.

Conclusions: This study showed that HRQoL of patients with stable or unstable CAD was moderate. Various patient characteristics appear to be significantly associated with HRQoL. Knowledge of these associations can help to identify ways to improve care (e.g. increase physical activity) and thereby improve HRQoL.

INTRODUCTION

Despite improvements in the treatment of cardiovascular disease (CVD) it still remains the second leading cause of death and disability across the Western world[106]. Patients with coronary artery disease (CAD), accounting for the largest proportion (25%) of deaths within CVD[106], are known to have a reduced quality of life compared with the general population[5,6]. Moreover, these patients often suffer from other disorders such as diabetes mellitus or obesity, which may lead to further loss in quality of life.

Quality of life is a subjective measure of overall well-being and reflects how a disease and its symptoms are perceived by a patient. Health-related quality of life (HRQoL) is often measured with generic questionnaires such as the EuroQol 5D (EQ-5D) or the Short Form (SF) 36. Various studies have already examined the HRQoL of patients with CAD[107-109]. Most of these studies have focused on the SF 36 with its physical (PCS) and mental component scores (MCS) or the preference based utility measure EQ-5D. The most common aim of those studies was to evaluate the impact of cardiovascular interventions like percutaneous coronary intervention or coronary artery bypass graft (CABG) on HRQoL. In contrast, only a handful of studies have evaluated the baseline HRQoL of patients before treatment and the relationship between HRQoL and baseline characteristics.

Poor HRQoL also seems to be associated with long-term morbidity and mortality. Therefore, insight into the patient characteristics which are associated with poor HRQoL may help to identify ways in which patient care can be improved. De Smedt et al. examined the relationship between patient characteristics and HRQoL but measured HRQoL at least 6 months after hospitalisation[110]. Furthermore, they used the two component scores of the SF-36 and the EQ-VAS, which are non-preference based measures while other methods such as the SF-6D are preferred for estimating the HRQoL[111]. Xie et al. compared patient characteristics and HRQoL measured with the SF-36 component scores, EQ-5D and EQ-VAS between coronary heart disease and non-coronary heart disease patients but did not study the associations between patient characteristics and HRQoL[112]. Van Stel et al. estimated the HRQoL of CAD patients using both the SF-6D and the EQ-5D[113], but the aim of their study was to compare the instruments and not to identify associations between HRQoL and patient characteristics. Therefore, the goal of this study is to estimate comprehensively HRQoL with both the SF-6D and the two SF-36 component scores for patients with CAD. The secondary aim of our study is to describe the associations between the SF-6D and routinely collected patient characteristics which could help to optimize care and consequently HRQoL.

METHODS

Study design

The HRQoL of patients with stable or unstable CAD was measured as part of the Circulating Cells prospective cohort study, which has the aim of identifying patients who are at an increased risk of developing a cardiovascular event by identifying markers that are associated with the instability of atherosclerotic plaque. In this study, patients undergoing a coronary angiography were included if they had known or suspected stable or unstable CAD; specific diagnoses included unstable angina and non-ST elevation MI (NSTEMI). Patients with serious concomitant disease, serious recent infectious disease (in the last 6 weeks) or suspected elevated state of the immune system were excluded. The study was approved by the medical ethical committees of the participating centers and conforms to the Declaration of Helsinki. All patients received oral and written information about the objectives of the study and provided written informed consent. More details about the Circulating Cells cohort study design can be found in a previous publication[85].

Health related quality of life measurement

Baseline HRQoL was measured using the Short Form (SF) 36 questionnaire, which contains 36 questions and eight dimensions[114]. The SF-6D is a revised version of the SF-36 and focuses on six domains: physical functioning, role participation, social functioning, bodily pain, mental health, and vitality each with between two and six levels[114]. 249 of all possible health states were valued by the general public with the standard gamble technique. HRQoL was estimated for each patient and associations with baseline patient characteristics were identified.

Beside the SF-6D estimates we have also estimated the PCS and MCS. These sex dependent scores, developed by Aaronson et al., estimate the means and the standard deviations (SD) for the general population for each of the eight domains: general health, physical functioning, role physical, role emotional, social functioning, bodily pain, vitality, mental health[115]. Furthermore, the individual scores for each dimension are also estimated. Patients were asked to complete the SF-36 questionnaire immediately after the coronary angiography and before treatment decision.

Statistical analyses

HRQoL and component scores were compared between patient subgroups determined by diagnosis. The following baseline characteristics were also collected during the study: age, gender, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), thrombolysis in myocardial infarction (TIMI) score for unstable CAD patients, New York Heart Association (NYHA) class, cardiac history [heart failure, previous MI, previous percutaneous transluminal coronary angioplasty (PTCA), and previous CABG), non-cardiac history (cerebrovascular accident (CVA) or transient ischaemic attack (TIA), pulmonary disease, peripheral vessel disease (PVD), and renal failure], and CVD risk factors (diabetes mellitus, hypertension, smoking, and pack years).

Multiple imputation was used to reduce the number of patients that could not be included in the analyses due to missing values. Missing values of patients who had filled in at least 75% of all SF-36 questions were imputed. Baseline characteristics (SBP, DBP, BMI, NYHA, previous heart failure, previous MI, CVA or TIA, pulmonary disease, PVD, renal failure, diabetes mellitus, hypertension, hyperlipidaemia, current smoker and pack years) were missing for less than 2% of all cases except for pack years which was missing for 6.6% of all cases. These characteristics and missing values of the SF-36 questionnaire (missing for less than 8.2%) were imputed using predictive mean matching for scale variables. Five imputation sets were created with ten iterations each using fully conditional specification in SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Age, gender, previous PTCA, previous CABG, and diagnosis were only used as predictors and not imputed since there were no missing values for these variables.

T-tests and ANOVA were used to test for differences between groups (e.g. diagnosis) for continuous variables. The Chi-square test was used to test for differences between groups for categorical variables.

Bivariate analyses using linear regression were performed to identify variables that were associated with HRQoL and component scores; stable and unstable CAD patients were analysed separately. Backwards selection was used to create the final multivariate models and stepwise selection was used to validate the selection of variables. P values lower than 0.05 were considered statistically significant, although a higher threshold of 0.10 was used to select variables for the multivariate analysis.

RESULTS

In total, 714 patients were included in the Circulating Cells cohort, 22 of whom were excluded from the analyses since they did not have significant coronary atherosclerosis. Of the remaining 692 patients, 465 answered at least one question in the questionnaire. HRQoL could not be assessed for 53 patients due to missing values. Baseline characteristics of the patients with a complete questionnaire (N=412) and the patients with an incomplete questionnaire (N=53) are presented in Table 5.1. The characteristics of the two groups were comparable, except for age, which significantly differed (Table 5.1). Multiple imputation was subsequently used to reduce the number of patients that were missing, which resulted in a population of 441 patients. Eighty-one percent of the patients with a completed questionnaire were diagnosed with stable angina including patients with silent ischemia. The frequency of current smokers in the unstable CAD population (N=85) were significantly ($p<0.01$) different to the frequency of current smokers in the stable CAD population (N=356) (Table 5.1). Furthermore, age and NYHA class significantly differed between the groups.

Tables 5.2 and 5.3 present the SF-6D, PCS, and MCS estimates for the total population, as well as the results for the stable and unstable CAD populations separately. The SF-6D index of all patients was 0.671 (SD: 0.134). The SF-6D scores were significantly associated with the diagnosis (stable/unstable), gender, SBP, BMI, previous PTCA, previous CVA or TIA, pulmonary disease, PVD, diabetes, hypertension, and pack years (Table 5.2). Male patients and patients with a high SBP reported a higher SF-6D score than female patients and patients with lower SBP; the other variables had a negative effect on SF-6D. SF-6D of the stable CAD group (0.663±0.132) was associated with almost the same characteristics as for the total population. Diabetes mellitus and hypertension were not significantly associated with SF-6D but NYHA class was. Patients with unstable CAD had a higher SF-6D score (0.704±0.136) than patients with stable CAD; PVD and previous CVA or TIA were negatively associated with the SF-6D. The mean PCS and MCS scores of patients with stable CAD were 40.20 and 44.25, respectively (Table 5.3). The unstable CAD group had a higher average PCS and MCS than the stable CAD group, which was in line with the HRQoL outcomes. Furthermore, unstable CAD patients also had higher average scores on each dimension than stable CAD patients. The mental health dimension had in both subgroups the highest score and the role physical dimension had the lowest score and was the most affected dimension by CVD compared to the general population[115]. Bivariate analyses performed on the total population (Tables S5.1 and S5.2) showed that diagnosis, previous PTCA, pack years, and previous CVA/TIA were all associated with both PCS and MCS. Other baseline characteristics, risk factors and non-cardiac history were also significantly associated with PCS or MCS.

Multivariate analyses showed that 15% of the variation in SF-6D scores in the stable CAD group could be explained by gender, SBP, BMI, previous PTCA, peripheral vessel disease, and pulmonary disease (Table 5.4). For unstable CAD patients, multivariate analyses showed that a previous CVA or TIA was significantly associated with SF-6D and explained 6% of the variation. Multivariate analyses were performed for both PCS and MCS scores and the results are presented in Tables S5.3 & S5.4.

Table 5.1 | Baseline characteristics

	Patients with an incomplete questionnaire			Patients with a complete questionnaire (without imputation)			Patients after imputation			Patients with stable CAD after imputation			Patients with unstable CAD after imputation				
	mean	sd	N[c]	mean	sd	N[c]	mean	sd	N[c]	mean	sd	N[c]	mean	sd	N[c]	p value[a]	p value[b]
Baseline characteristics																	
Age	67	9	53	62	9	412	63	10	441	63	9	356	60	10	85	**0.001**	**0.017**
Male (%)	68%		53	69%		412	69%		441	69%		356	68%		85	0.825	0.837
SBP (mmHg)	138	19	52	135	19	408	135	19	441	135	20	356	132	19	85	0.270	0.190
DBP (mmHg)	77	13	52	77	10	408	77	11	441	77	5	356	79	9	85	0.551	0.172
BMI (kg/m2)	27	5	53	28	5	405	28	4	441	28	4	356	27	5	85	0.176	0.127
TIMI score[d]																0.055	NA
1	9%		11	6%		77	6%		83				6%		83		
2	9%		11	30%		77	28%		83				28%		83		
3	18%		11	31%		77	31%		83				31%		83		
4	27%		11	19%		77	19%		83				19%		83		
5	18%		11	12%		77	12%		83				12%		83		
6	9%		11	1%		77	2%		83				2%		83		
7	9%		11	0%		77	1%		83				1%		83		
NYHA																0.400	**p<0.001**
NYHA I	66%		53	67%		411	66%		441	66%		356	68%		85		
NYHA II	15%		53	21%		411	21%		441	24%		356	8%		85		
NYHA III	13%		53	8%		411	8%		441	10%		356	1%		85		
NYHA IV	6%		53	4%		411	4%		441	0%		356	22%		85		

Table 5.1 | *(Continued)*

	Patients with an incomplete questionnaire			Patients with a complete questionnaire (without imputation)			Patients after imputation			Patients with stable CAD after imputation			Patients with unstable CAD after imputation				
	mean	sd	N[c]	mean	sd	N[c]	mean	sd	N[c]	mean	sd	N[c]	mean	sd	N[c]	p value[a]	p value[b]
Cardiac history (%)																	
Previous heart failure	8%		53	3%		411	4%		441	4%		356	2%		85	0.142	0.472
Previous MI	30%		53	29%		412	29%		441	30%		356	21%		85	0.852	0.088
Previous PTCA	38%		53	37%		412	37%		441	38%		356	32%		85	0.960	0.290
Previous CABG	15%		53	8%		412	8%		441	9%		356	7%		85	0.087	0.622
Non-cardiac history (%)																	
CVA/TIA	8%		53	6%		411	6%		441	6%		356	9%		85	0.678	0.214
Pulmonary disease	9%		53	11%		411	11%		441	11%		356	12%		85	0.738	0.796
PVD	15%		53	12%		411	12%		441	12%		356	11%		85	0.508	0.682
Renal failure	6%		53	2%		411	2%		441	3%		356	1%		85	0.062	0.426
Risk factors (%)																	
Diabetes mellitus	19%		53	23%		411	22%		441	22%		356	21%		85	0.602	0.930
Hypertension	64%		53	66%		409	66%		441	68%		356	58%		85	0.435	0.083
Hyperlipidaemia	72%		53	70%		410	70%		441	71%		356	67%		85	0.799	0.474
Current smokers (%)	26%		53	20%		411	20%		441	17%		356	32%		85	0.255	**p<0.01**
Pack years[e]	17	15	50	21	19	385	20	20	441	20	19	356	21	21	85	0.335	0.757
Diagnosis (%)																**0.775**	**NA**
Stable angina	79%		53	81%		412	81%		441								
Unstable angina	9%		53	11%		412	11%		441								
NSTEMI	11%		53	8%		412	9%		441								

Table 5.1 | *(Continued)*

	Patients with an incomplete questionnaire			Patients with a complete questionnaire (without imputation)			Patients after imputation			Patients with stable CAD after imputation			Patients with unstable CAD after imputation				
	mean	sd	N[c]	mean	sd	N[c]	mean	sd	N[c]	mean	sd	N[c]	mean	sd	N[c]	p value[a]	p value[b]
Indicated for treatment																	0.496
PCI	72%		53	67%		412	67%		441	67%		356	68%		85		
CABG	6%		53	11%		412	10%		441	10%		356	13%		85		
Medication	23%		53	23%		412	23%		441	23%		356	19%		85		

[a] P value for comparison: complete vs. incomplete questionnaire; [b] P value for comparison: stable CAD vs. unstable CAD; [c] Number of patients on which the analyses were based; [d] Only reported for unstable angina and NSTEMI; [e] Number of packs per day multiplied with years of smoking

BMI: body mass index; CABG: coronary artery bypass graft; CVA: cerebrovascular accident; DBP: diastolic blood pressure; MI: myocardial infarction; NSTEMI: non ST elevation myocardial infarction; NYHA: New York heart association; PTCA: percutaneous transluminal coronary angioplasty; PVD: peripheral vessel disease; SBP: systolic blood pressure; TIA: transient ischaemic attack; TIMI: thrombolysis in myocardial infarction

Table 5.2 | Associations with quality of life SF-6D

	Total population				Stable CAD population				Unstable CAD population			
	Mean	**SD**	**N**	**p value**	**Mean**	**SD**	**N**	**p value**	**Mean**	**SD**	**N**	**p value**
Overall	0.671	0.134	441		0.663	0.132	356		0.704	0.136	85	
Diagnosis				**0.002**								
Stable CAD	0.663	0.132	356									
Unstable angina	0.672	0.120	47									
NSTEMI	0.743	0.146	38									
Treatment indication				0.761				0.832				0.772
PCI	0.674	0.136	297		0.665	0.135	239		0.708	0.135	58	
CABG	0.661	0.129	45		0.656	0.115	34		0.677	0.174	11	
Medication	0.666	0.131	99		0.657	0.134	83		0.708	0.117	16	
Baseline characteristics												
Age (years)	0.001*		441	0.062	0.001*		356	0.063	0.002*		85	0.246
Gender				**p<0.001**				**p<0.001**				0.389
Male	0.687	0.133	305		0.681	0.133	247		0.713	0.132	58	
Female	0.634	0.128	136		0.621	0.121	109		0.685	0.140	27	
SBP (mmHg)	0.001*		441	**0.035**	0.001*		356	**0.041**	0.001*		85	0.312
DBP (mmHg)	0.001*		441	0.297	0.001*		356	0.459	0.001*		85	0.606
BMI (kg/m^2)	-0.007*			**p<0.001**	-0.006*			**p<0.001**	-0.006*			0.121
TIMI score[a]				0.531								0.531
1	0.655	0.132	5						0.655	0.132	5	
2	0.717	0.126	23						0.717	0.126	23	
3	0.666	0.135	26						0.666	0.135	26	
4	0.728	0.146	16						0.728	0.146	16	
5	0.701	0.149	10						0.701	0.149	10	
6+7	0.770	0.067	3						0.770	0.067	3	

Table 5.2 | *(Continued)*

	Total population				Stable CAD population				Unstable CAD population			
	Mean	**SD**	**N**	**p value**	**Mean**	**SD**	**N**	**p value**	**Mean**	**SD**	**N**	**p value**
NYHA				0.059				**0.04**				0.355
NYHA I	0.680	0.137	293		0.675	0.136	235		0.703	0.139	58	
NYHA II	0.643	0.119	93		0.643	0.122	86		0.643	0.093	7	
NYHA III & IV	0.664	0.137	55		0.628	0.121	35		0.728	0.141	20	
Cardiac history												
Previous heart failure				0.395				0.399				0.962
yes	0.643	0.132	16		0.634	0.135	14		0.709	0.120	2	
no	0.672	0.134	425		0.664	0.133	342		0.704	0.137	83	
Previous MI				0.972				0.741				0.892
yes	0.671	0.127	127		0.666	0.123	109		0.700	0.146	18	
no	0.670	0.137	314		0.661	0.136	247		0.705	0.134	67	
Previous PTCA				**0.011**				**0.006**				0.943
yes	0.650	0.136	162		0.638	0.132	135		0.706	0.143	27	
no	0.683	0.131	279		0.678	0.130	221		0.703	0.134	58	
Previous CABG				0.775				0.589				0.591
yes	0.665	0.128	37		0.651	0.121	31		0.733	0.152	6	
no	0.671	0.134	404		0.664	0.133	325		0.702	0.135	79	
Non-cardiac history												
CVA/TIA				**p<0.001**				**0.006**				**0.011**
yes	0.585	0.126	28		0.582	0.133	20		0.590	0.122	8	
no	0.677	0.132	413		0.668	0.131	336		0.716	0.132	77	
Pulmonary disease				**p<0.001**				**p<0.001**				0.344
yes	0.601	0.108	48		0.584	0.104	38		0.666	0.104	10	
no	0.679	0.134	393		0.672	0.132	318		0.709	0.140	75	

Table 5.2 | *(Continued)*

	Total population				Stable CAD population				Unstable CAD population			
	Mean	**SD**	**N**	**p value**	**Mean**	**SD**	**N**	**p value**	**Mean**	**SD**	**N**	**p value**
PVD				**p<0.01**				**0.011**				**0.041**
yes	0.615	0.123	52		0.615	0.332	43		0.616	0.116	9	
no	0.678	0.135	389		0.669	0.133	313		0.714	0.135	76	
Renal failure				0.08				0.152				0.311
yes	0.594	0.120	10		0.597	0.127	9		0.568		1	
no	0.672	0.134	431		0.664	0.133	347		0.706	0.136	84	
Risk factors												
Diabetes mellitus				**0.028**				0.118				0.067
yes	0.645	0.134	97		0.642	0.134	78		0.654	0.131	19	
no	0.678	0.133	344		0.668	0.132	278		0.718	0.135	66	
Hypertension				**0.037**				0.119				0.268
yes	0.661	0.131	290		0.655	0.132	241		0.690	0.133	49	
no	0.689	0.138	151		0.679	0.135	115		0.723	0.140	36	
Hyperlipidaemia				0.167				0.268				0.676
yes	0.665	0.134	310		0.658	0.134	253		0.697	0.126	57	
no	0.684	0.136	131		0.675	0.127	103		0.718	0.156	28	
Current smokers				0.141				0.195				0.148
yes	0.652	0.138	89		0.643	0.134	62		0.673	0.148	27	
no	0.675	0.132	352		0.667	0.131	294		0.718	0.128	58	
Pack years[b]	-0.001*		441	**0.015**	-0.001*		356	**0.023**	-0.001*		85	0.313

[a] Only for unstable angina and NSTEMI; [b] Number of packs per day multiplied with years of smoking; * Coefficient

BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CVA: cerebrovascular accident; DBP: diastolic blood pressure; MI: myocardial infarction; NSTEMI: non ST elevation myocardial infarction; NYHA: New York heart association; PTCA: percutaneous transluminal coronary angioplasty; PVD: peripheral vessel disease; SBP: systolic blood pressure; TIA: transient ischaemic attack; TIMI: thrombolysis in myocardial infarction

Table 5.3 | SF-36 scores (domains and component scores)

	Total (N=441)		Stable CAD (N=356)		Unstable CAD (N=85)		General population (men, N=976)		General population (women, N=766)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p value*
Dimensions											
General health	57.67	21.26	57.29	21.10	59.29	22.02	71.6	20.6	69.9	20.6	0.44
Physical functioning	62.93	27.53	61.65	27.32	68.67	27.95	85.4	21.0	80.4	24.2	0.04
Role physical	38.88	44.30	37.12	43.90	46.24	44.96	78.7	34.1	73.8	38.5	0.10
Role emotional	61.56	44.12	59.64	44.37	68.57	42.92	85.5	29.9	78.5	35.7	0.10
Social functioning	65.06	26.75	63.67	26.91	70.88	25.40	86.0	21.1	82.0	23.5	0.04
Bodily pain	60.86	26.38	60.05	26.36	64.27	26.32	77.3	22.7	71.9	23.8	0.22
Vitality	53.34	22.51	52.28	22.47	57.79	21.13	71.9	18.3	64.3	19.7	0.07
Mental health	70.70	19.50	69.87	19.76	74.16	17.71	79.3	16.4	73.7	18.2	0.08
Composite scores											
PCS	40.58	10.82	40.20	10.60	42.18	11.64	50	10	50	10	0.52
MCS	44.81	12.01	44.25	12.11	47.15	11.34	50	10	50	10	0.23

* p value stable vs. unstable

PCS: Physical component score; MCS: Mental component score

Table 5.4 | Associations between patient characteristics and SF-6D

Stable CAD (N=356)	Bivariate analyses	Multivariate analyses	p value[a]
Age (per year)	0.001		
Male	0.060	0.062	p<0.001
SBP (per mmHg)	0.001	0.0003	0.008
BMI (kg/m^2)	-0.006	-0.005	0.001
NYHA class			
NYHA class I	ref		
NYHA class II (vs. NYHA class I)	-0.032		
NYHA class III (vs. NYHA class I)	-0.047		
Previous PTCA	-0.039	-0.040	0.003
CVA/TIA	-0.085		
Pulmonary disease	-0.088	-0.071	0.001
Peripheral vessel disease	-0.054	-0.044	0.028
Pack years[b]	-0.001		
Constant		0.666	p<0.001
Adjusted R^2		15%	
Unstable CAD (N=81)			
CVA/TIA	-0.126	-0.126	0.010
Peripheral vessel disease	-0.098		
Diabetes	-0.064		
Constant		0.716	p<0.001
Adjusted R^2		6%	

[a] P value of multivariate analyses; [b] Number of packs per day multiplied with years of smoking
SBP: systolic blood pressure; BMI: body mass index; NYHA: New York heart association; PTCA: percutaneous transluminal coronary angioplasty; CVA: cerebrovascular accident; TIA: transient ischaemic attack

DISCUSSION

This study estimated the baseline SF-6D score and both the physical and mental component scores for patients with stable or unstable CAD with the SF-6D and SF-36, respectively. Furthermore, we showed associations between baseline characteristics (e.g. gender, diagnosis, (non-)cardiac history, and risk factors) and SF-6D, PCS, and MCS. As shown in other studies, the mental health dimension was the least affected dimension of the SF-36 and, as expected, CAD had a particularly negative association with the physical dimensions.

Bivariate analyses showed a negative association between age and PCS. In contrast, age was positively but not significantly associated with MCS but this association was also identified

before[110,112]. Furthermore, similar relationships between the component scores with gender, diabetes, history of stroke, smoking, and raised blood pressure were identified as reported in De Smedt et al.[110] and Emery et al.[108]. Besides these associations we also found that non-cardiac history (e.g. pulmonary disease, PVD and renal failure) and other risk factors (e.g. hypertension and hyperlipidaemia) were associated with both PCS and MCS. Covariates were in general more strongly associated with PCS than with MCS. For HRQoL, measured with the SF-6D, similar associations were present: gender, SBP, BMI, previous PTCA, non-cardiac history (e.g. CVA/TIA, PVD or pulmonary disease), diabetes mellitus, hypertension, and pack-years.

Implications

The HRQoL, measured with the SF-6D index, of the included patients was 0.67±0.13 compared with 0.85±0.17, measured with the EQ-5D, in the general population within the same age category[116]. Quality of life can be improved by optimizing care for patients with stable or unstable CAD using our results. During the workup, it could be useful to measure the HRQoL of these patients as a standard part of their care. Dimension specific care can be provided to patients with lower scores in those dimensions. The results from this study suggest that CAD patients should receive more care that focuses on the 'role physical' dimension. For example, patients could be encouraged to increase physical activity which is in line with current European Society of Cardiology guidelines[20]. Other characteristics found in this study to be associated with a lower HRQoL (BMI, smoking) can be addressed by encouraging patients to adopt healthier lifestyle behaviours.

Furthermore, these results from this study can be used by researchers to estimate the HRQoL in their population as part of a cost-effectiveness analysis of CVD interventions. However, patient characteristics of the Circulating Cells cohort need to be transferable with the population under consideration in the economic analysis.

Limitations

Multiple imputation was performed for patients who completed 75% or more of the SF-36 questionnaire since some patients started with the questionnaire but were reluctant to continue. Twenty-four patients of the 465 patients were not included in the analyses; on average they had filled in the questionnaire for 47% of all questions. These 24 patients were on average older than the analysed population (N=441). Brazier et al. have also recognized that the extent of missing data of SF-36 specific dimensions was significantly associated with age[117]. It is possible that a selection effect could have occurred by removing those 24 cases from the analyses; since they were unable to fill in the questionnaire. Consequently, the estimated HRQoL of the patients could be lower in practice but excluding only 5% of the cases from the analyses has probably a minimal effect.

Most of the patients (81%) that were included in this study were diagnosed with stable CAD, meaning that a relatively small group of patients had unstable CAD. This reduced power to identify existing associations between HRQoL and patient characteristics may explain why only a few characteristics were significantly associated with HRQoL and health status. Surprisingly, unstable CAD patients had on average a higher HRQoL than patients with stable CAD. This association can be the result of a selection effect. However, Hlatky et al.[118] have also shown that stable angina patients with CCS class 3 or 4 have a lower HRQoL than unstable patients.

In our study we used the United Kingdom (UK) decrements to calculate the SF-6D index scores since there is no set of values available for The Netherlands. However, we do not expect substantial differences in the valuation of health states between the Netherlands and the UK. PCS and MCS scores are normalized with Dutch gender-specific dimension scores[115].

One possible limitation of the SF-36 is that the answer possibilities are assumed to have the same impact on HRQoL. For example, the answer possibilities of questions concerning how limited patients are in daily activities are possibly not linear. Other limitations of using the SF-36 in CAD patients have been described thoroughly by Brazier et al.[117]. However, the benefit of using a preference-based instrument is the ability to compare the impact that various diseases have on HRQoL.

Conclusion

This study showed that HRQoL of patients with stable or unstable CAD was moderate. Various patient characteristics appear to be significantly associated with HRQoL, even after adjustment for other factors. Knowledge of these associations can help to identify ways to improve care and thereby improve HRQoL. At the very least, this knowledge should stimulate more discussion about the needs of patients that are currently being inadequately addressed.

Table S5.1 | Associations with PCS

	Total population				Stable CAD population				Unstable CAD population			
	Mean / intercept	**SD**	**N**	**p value**	**Mean / intercept**	**SD**	**N**	**p value**	**Mean / intercept**	**SD**	**N**	**p value**
Overall	40.583	10.824	441		40.201	10.598	356		42.183	11.642	85	
Diagnosis				**0.023**								
Stable CAD	40.201	10.598	356									
Unstable angina	39.777	11.111	47									
NSTEMI	45.159	11.750	38									
Indicated for treatment				0.879				0.747				0.934
PCI	40.758	10.782	297		40.488	10.753	239		41.870	10.900	58	
CABG	40.135	11.757	45		39.311	10.463	34		42.683	15.340	11	
Medication	40.264	10.734	99		39.742	10.412	83		42.973	12.236	16	
Baseline characteristics												
Age (years)	-0.043			0.433	-0.038			0.522	-0.015			0.912
Gender				0.106				**0.029**				0.710
Male	41.138	11.066	305		40.968	10.992	247		41.861	11.397	58	
Female	39.340	10.206	136		38.464	9.480	109		42.876	12.348	27	
SBP (mmHg)	0.061		441	**0.021**	0.082			**0.004**	-0.018			0.789
DBP (mmHg)	0.129		441	**0.008**	0.140			**0.007**	0.037			0.785
BMI (kg/m^2)	-0.600		441	**p<0.001**	-0.524			**p<0.001**	-0.858			**0.004**
TIMI score[a]												0.221
1									46.687	17.488	5	
2									44.709	10.587	23	
3									37.660	11.406	26	

Table S5.1 | *(Continued)*

	Total population				Stable CAD population				Unstable CAD population			
	Mean / intercept	**SD**	**N**	**p value**	**Mean / intercept**	**SD**	**N**	**p value**	**Mean / intercept**	**SD**	**N**	**p value**
4									43.375	11.800	16	
5									39.605	9.933	10	
6 + 7									47.107	7.216	3	
NYHA				**0.044**				**0.011**				0.102
NYHA I	41.413	10.900	293		41.361	10.874	235		41.624	11.116	58	
NYHA II	38.221	9.813	93		38.427	9.591	86		35.684	12.910	7	
NYHA III & IV	40.158	11.661	55		36.774	10.170	35		46.079	11.986	20	
Cardiac history												
Previous heart failure				0.077				0.061				0.903
yes	35.921	11.540	16		35.178	11.015	15		41.186	17.177	2	
no	40.761	10.787	425		40.410	10.645	345		42.207	11.629	83	
Previous MI				0.380				0.783				0.21
yes	39.869	11.274	127		39.990	11.186	109		39.141	11.568	18	
no	40.871	10.655	314		40.294	10.472	251		43.000	11.611	67	
Previous PTCA				**0.002**				**0.003**				0.284
yes	38.503	10.502	162		38.164	10.514	136		40.196	10.586	27	
no	41.791	10.838	279		41.446	10.554	224		43.108	12.093	58	
Previous CABG				0.101				0.061				0.773
yes	37.787	9.475	37		36.679	9.469	31		43.511	8.363	6	
no	40.839	10.910	404		40.537	10.728	329		42.082	11.889	79	

Table S5.1 | *(Continued)*

	Total population				Stable CAD population				Unstable CAD population			
	Mean / intercept	SD	N	p value	Mean / intercept	SD	N	p value	Mean / intercept	SD	N	p value
Non-cardiac history												
CVA/TIA				**p<0.001**				**0.001**				0.055
yes	33.210	10.950	28		32.598	11.044	21		34.768	11.097	8	
no	41.091	10.642	413		40.663	10.485	339		42.953	11.497	77	
Pulmonary disease				**p<0.001**				**p<0.001**				**0.005**
yes	32.515	9.665	48		31.715	10.043	39		35.589	7.253	10	
no	41.578	10.596	393		41.228	10.295	321		43.062	11.867	75	
PVD				**p<0.001**				**0.002**				0.098
yes	35.591	10.794	52		35.469	10.787	43		36.181	11.533	9	
no	41.257	10.660	389		40.859	10.508	317		42.894	11.525	76	
Renal failure				**p<0.001**				**0.002**				0.324
yes	29.728	9.359	10		29.615	9.831	9		30.781		1	
no	40.846	10.739	431		40.488	10.590	351		42.319	11.644	84	
Risk factors												
Diabetes mellitus				**0.012**				0.079				**0.006**
yes	38.168	10.176	97		38.706	10.267	80		35.959	10.065	19	
no	41.265	10.927	344		40.621	10.751	280		43.975	11.507	66	
Hypertension				**0.019**				0.157				**0.01**
yes	39.710	10.673	290		39.747	10.519	243		39.527	11.671	49	
no	42.254	10.977	151		41.147	10.902	117		45.799	10.740	36	

Table S5.1 | *(Continued)*

	Total population				Stable CAD population				Unstable CAD population			
	Mean / intercept	**SD**	**N**	**p value**	**Mean / intercept**	**SD**	**N**	**p value**	**Mean / intercept**	**SD**	**N**	**p value**
Hyperlipidaemia				**0.028**				0.122				0.07
yes	39.851	10.725	310		39.682	10.767	256		40.602	11.070	57	
no	42.312	10.850	131		41.474	10.362	104		45.402	12.304	28	
Current smokers				0.865				0.919				0.413
yes	40.409	10.718	89		40.298	10.132	62		40.664	12.145	27	
no	40.628	10.864	352		40.181	10.804	298		42.890	11.437	58	
Pack years[b]	-0.064			**0.026**	-0.058			0.058	-0.088			0.221

[a] Only for unstable angina and NSTEMI; [b] Number of packs per day multiplied with years of smoking

BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CVA: cerebrovascular accident; DBP: diastolic blood pressure; MI: myocardial infarction; NSTEMI: non ST elevation myocardial infarction; NYHA: New York heart association; PTCA: percutaneous transluminal coronary angioplasty; PVD: peripheral vessel disease; SBP: systolic blood pressure; TIA: transient ischaemic attack; TIMI: thrombolysis in myocardial infarction

Table S5.2 | Associations with MCS

	Total population				Stable CAD population				Unstable CAD population			
	Mean / intercept	SD	N	p value	Mean / intercept	SD	N	p value	Mean / intercept	SD	N	p value
Overall	44.810	12.012	**441**		44.252	12.111	356		47.148	11.336	85	
Diagnosis				**0.047**								
Stable CAD	44.252	12.111	356									
Unstable angina	45.458	12.296	47									
NSTEMI	49.238	9.748	38									
Indicated for treatment				0.262				0.195				0.883
PCI	45.419	11.888	297		45.000	11.897	239		47.144	11.701	58	
CABG	44.413	11.851	45		43.946	12.071	34		45.853	11.410	11	
Medication	43.166	12.638	99		42.224	12.856	83		48.053	10.359	16	
Baseline characteristics												
Age (years)	0.234			**p<0.001**	0.259			**p<0.001**	0.217			0.085
Gender				0.436				0.59				0.514
Male	44.512	12.512	305		44.022	12.713	247		46.599	11.415	58	
Female	45.480	10.915	136		44.774	10.732	109		48.328	11.232	27	
SBP (mmHg)	0.013		441	0.660	-0.002			0.956	0.100			0.125
DBP (mmHg)	-0.063		441	0.239	-0.098			0.094	0.090			0.496
BMI (kg/m^2)	-0.249		441	0.057	-0.292			**0.046**	0.020			0.945
TIMI score[a]												0.802
1									42.281	12.562	5	
2									47.481	11.961	23	
3									46.776	11.169	26	

Table S5.2 | *(Continued)*

	Total population				Stable CAD population				Unstable CAD population			
	Mean / intercept	SD	N	p value	Mean / intercept	SD	N	p value	Mean / intercept	SD	N	p value
4									46.117	11.196	16	
5									47.416	12.626	10	
6 + 7									54.570	4.978	3	
NYHA				0.182				0.293				0.916
NYHA I	45.425	12.183	293		44.923	12.448	235		47.458	10.831	58	
NYHA II	42.793	11.488	93		42.552	11.208	86		45.760	15.246	7	
NYHA III & IV	44.945	11.950	55		43.922	12.158	35		46.735	11.811	20	
Cardiac history												
Previous heart failure				0.865				0.790				0.967
yes	45.308	9.801	16		45.095	10.486	14		46.822	2.074	2	
no	44.791	12.104	425		44.217	12.201	342		47.156	11.471	83	
Previous MI				0.613				0.449				0.936
yes	45.266	11.411	127		44.985	11.585	109		46.957	9.654	18	
no	44.627	12.237	314		43.930	12.340	247		47.199	11.805	67	
Previous PTCA				**0.014**				**0.034**				0.282
yes	42.888	13.215	162		42.423	13.542	135		45.213	11.386	27	
no	45.926	11.153	279		45.369	11.095	221		48.049	11.266	58	
Previous CABG				0.532				0.444				0.924
yes	46.005	11.537	37		45.866	11.234	31		46.724	14.150	6	
no	44.701	12.096	404		44.098	12.226	325		47.180	11.198	79	

Table S5.2 – *(Continued)*

	Total population				Stable CAD population				Unstable CAD population			
	Mean / intercept	SD	N	p value	Mean / intercept	SD	N	p value	Mean / intercept	SD	N	p value
Non-cardiac history												
CVA/TIA				**0.03**				**0.063**				0.117
yes	40.103	11.556	28		39.659	11.460	20		41.233	12.585	8	
no	45.134	12.004	413		44.531	12.120	336		47.762	11.115	77	
Pulmonary disease				0.094				0.31				0.424
yes	42.082	11.518	48		41.462	11.179	38		44.459	13.139	10	
no	45.147	12.071	393		44.589	12.228	318		47.506	11.112	75	
PVD				0.161				0.265				0.387
yes	42.631	11.158	52		42.335	11.474	43		44.058	9.882	9	
no	45.104	12.110	389		44.518	12.185	313		47.514	11.511	76	
Renal failure				0.754				0.875				0.180
yes	43.647	8.788	10		44.868	8.283	9		32.182		1	
no	44.838	12.085	431		44.235	12.206	347		47.326	11.283	84	
Risk factors												
Diabetes mellitus				0.092				0.055				0.922
yes	42.995	12.802	97		41.928	13.306	78		47.373	9.591	19	
no	45.322	11.757	344		44.904	11.725	278		47.083	11.827	66	
Hypertension				0.394				0.409				0.902
yes	44.457	12.150	290		43.883	12.408	241		47.278	10.609	49	
no	45.485	11.768	151		45.022	11.582	115		46.970	12.371	36	

Table S5.2 | *(Continued)*

	Total population				Stable CAD population				Unstable CAD population			
	Mean / intercept	**SD**	**N**	**p value**	**Mean / intercept**	**SD**	**N**	**p value**	**Mean / intercept**	**SD**	**N**	**p value**
Hyperlipidaemia				0.355				0.457				0.657
yes	44.464	12.365	310		43.945	12.462	253		46.766	11.722	57	
no	45.627	11.212	131		45.004	11.331	103		47.926	10.607	28	
Current smokers				**0.003**				**p<0.001**				0.357
yes	41.494	12.511	89		39.753	12.663	62		45.490	11.377	27	
no	45.649	11.733	352		45.201	11.789	294		47.920	11.311	58	
Pack years[b]	-0.089			**0.006**	-0.102			**0.004**	-0.047			0.481

[a] Only for unstable angina and NSTEMI; [b] Number of packs per day multiplied with years of smoking

BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; CVA: cerebrovascular accident; DBP: diastolic blood pressure; MI: myocardial infarction; NSTEMI: non ST elevation myocardial infarction; NYHA: New York heart association; PTCA: percutaneous transluminal coronary angioplasty; PVD: peripheral vessel disease; SBP: systolic blood pressure; TIA: transient ischaemic attack; TIMI: thrombolysis in myocardial infarction

Table S5.3 | Associations between patient characteristics and PCS

Stable CAD (N=360)	Bivariate analyses	Multivariate analyses	p value[a]
Male	2.504	2.450	0.027
SBP (mmHg)	0.082	0.099	p<0.001
DBP (mmHg)	0.140		
BMI (kg/m²)	-0.524	-0.393	0.001
NYHA class			
NYHA class I	ref		
NYHA class II	-2.934		
NYHA class III	-4.587	-3.802[c]	0.029
Heart failure	-5.232		
Previous PTCA	-3.282	-2.712	0.010
Previous CABG	-3.858		
CVA/TIA	-8.066		
Pulmonary disease	-9.513	-8.445	p<0.001
PVD	-5.390	-3.768	0.017
Renal artery disease	-10.874	-9.994	0.002
Pack years[b]	-0.058		
Constant		39.027	p<0.001
Adjusted R^2		20%	
Unstable CAD (N=81)			
BMI (kg/m²)	-0.858	-0.872	0.002
CVA/TIA	-8.158	-8.594	0.031
Pulmonary disease	-7.474	-7.191	0.040
Diabetes mellitus	-8.016		
Hypertension	-6.272		
Hyperlipidaemia	-4.799		
Constant		67.318	P<0.001
Adjusted R^2		17%	

[a] P value of multivariate analyses; [b] Number of packs per day multiplied with years of smoking
BMI: body mass index; CABG: coronary artery bypass graft; CVA: cerebrovascular accident; DBP: diastolic blood pressure; NYHA: New York heart association; PTCA: percutaneous transluminal coronary angioplasty; PVD: Peripheral vessel disease; SBP: systolic blood pressure; TIA: transient ischaemic attack

Table S5.4 | Associations between patient characteristics and MCS

Stable CAD (N=360)	**Bivariate analyses**	**Multivariate analyses**	**p value[a]**
Age	0.259	0.252	p<0.001
DBP (mmHg)	-0.098		
BMI (kg/m^2)	-0.292		
Previous PTCA	-2.946	-2.593	0.044
CVA/TIA	-4.872		
Diabetes mellitus	-2.976	-3.155	0.037
Current smoker	-5.448		
Pack years[b]	-0.102	-0.087	0.012
Constant		31.818	p<0.001
Adjusted R^2		7%	

[a] P value of multivariate analyses; [b] Number of packs per day multiplied with years of smoking

BMI: body mass index; DBP: diastolic blood pressure; PTCA: percutaneous transluminal coronary angioplasty; CVA: cerebrovascular accident; TIA: transient ischaemic attack


Challenges
Modelling
Cardiovascular
Technologies
Devices
Tests
Data
ICER
QALY
Analyses
Markov
Cost-effectiveness
Disease
Costs
Blood
Results
Extrapolating
CVD
Thesis
Intervention
CAD
PCI
Drugs
Diagnosis
Prevention
Angina
Specificity
Sensitivity Analyses
EVAR
RCT
Guidelines
TAVI
Fevar
Follow-up
Scenario Analyses
Structure
Precision
Validity
Bias
Outcomes
Risks
Stroke
Literature
Efficacy
Persistence
Identification
Methods
Survival
Frequency
Interaction
Statin
Accuracy
Importance
Synergy
Artery
Technologies
QoL
Decision Tree
Prior Likelihood
ICA
Statistics
Monitoring
Indication
Transition
Limitations
Gold Standard
False Negative
False Positive
True Negative
True Positive
Regression
Recommendations
Perspective
Short Term
Review
Observational
Probabilities
Learning Curve
Simplification
Diastolic
Systolic
Ischemic
Cerebrovascular
Care Pathway
Prevalence
Stenosis
Real-world
CABG
DES
Bevar
Balloon
Thrombosis
Treatment
Wait Time
Heart
Surgical
Prognostic
Effectiveness
Impact
Compliance
Bypass
Relative Risk
Budget
Management
History
CT-scanner
Heterogeneity
Cohort
Document Analysis
Plaque
Chance
Utilities
Clinical
Dynamic
AAA

Chapter 6

Using meta-regression analyses in addition to conventional systematic review methods to examine the variation in cost-effectiveness results – a case study

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Revisions BMC Health Services Research

ABSTRACT

Objectives: Systematic reviews of cost-effectiveness analyses summarize results and describe study characteristics. Variability in the study results is often explained qualitative or based on sensitivity analyses of individual studies. However, variability due to input parameters and study characteristics (e.g. funding or quality of the study) is often not statistically explained. As a case study, a systematic review on the cost-effectiveness of drug-eluting stents (DES) versus bare-metal stents (BMS) using meta-regression analyses will be performed to explore the usefulness of such methods compared with conventional review methods.

Methods: We identified and reviewed all modelling studies published until January 2012 that compared costs and consequences of DES versus BMS. We extracted general study information (e.g. funding), modelling methods, values of input parameters, and quality of the model (Philips). Associations between study characteristics and the incremental costs and effectiveness of individual analyses were explored using regression analyses corrected for study ID.

Results: Sixteen eligible studies were identified, with a combined total of 508 analyses. The overall quality of the models was moderate (59%±15%). This study showed associations (e.g. type of lesion) that were expected (based on individual studies), however the meta-regression analyses revealed also unpredicted associations: e.g. model quality was negatively associated with repeat revascularizations avoided.

Conclusions: Meta-regressions can be of added value, identifying significant associations that could not be identified using conventional review methods or by sensitivity analyses of individual studies. Furthermore, we indicated the need to examine input parameters and of performing a quality check of studies when interpreting the results.

INTRODUCTION

Economic evaluations are increasingly used to assist in decision making of interventions. Often for a specific certain decision problem many economic evaluations are conducted, the results of these studies often differ substantially between studies: from interventions being dominated to being dominant. Therefore, it is necessary that systematic reviews are performed to summarize the results of the individual economic evaluations. Besides summarizing the study characteristics and results it would be interesting to explain statistically the variability in the incremental costs and incremental effects and thus the conclusions. Differences can exist due to differences in values used for input parameters, perspective, time horizon and other factors. Some differences could easily be explained by the values that were used for the input parameters, since for some input parameters a linear relationship with the outcomes exists. For example, an increase in one-off intervention costs will lead to an increase in the incremental costs, ceteris paribus. Often these variations are explained by sensitivity analyses of individual studies. Other associations such as the influence of funding could be identified using meta-regression analyses in addition to conventional systematic review methods. Meta-regression analyses are currently used to combine the results of clinical trials and to investigate the effect of methodological diversity of the studies on the results[119]. To explain the variability in the incremental costs and incremental effects of cost-effectiveness analysis (CEA) it could be useful to apply these meta-regression analyses in systematic reviews of economic evaluations.

The aim of this study is to explore the usefulness of meta-regression analyses in systematically explaining the variability in the results compared with conventional review methods and sensitivity analyses of individual studies. Many economic evaluations have estimated the cost-effectiveness of drug-eluting stents (DES) versus bare-metal stents (BMS) for the treatment of patients with coronary artery disease. The results between the studies vary considerably, which makes this decision problem a good case study to explore if meta-regression analyses are of added value. Systematic reviews[91,120,121] on the cost-effectiveness of DES versus BMS have been performed but did not explore statistically the causes of the variability in incremental costs and incremental effects between the studies. Associations with the incremental outcomes (costs, quality-adjusted life years and repeat revascularizations avoided) will be identified in this study. Besides the 'known' factors (e.g. age, type of lesion, price of stents, relative risk repeat revascularisations avoided) explaining the cost-effectiveness of DES versus BMS we will identify associations that could only be identified at a meta-level such as the quality of the studies and funding.

METHODS

Inclusion and exclusion criteria

A systematic literature search was performed to identify all English-language publications (at any time before January 2012) of CEAs using decision analytic models to compare the costs and consequences of DES (sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), everolimus or zotarolimus-eluting stent (ZES)) versus BMS for patients who require a stent implantation due to an atherosclerotic lesion of the coronary artery. The effectiveness of the studies had to be expressed in quality adjusted life years (QALY) or in disease specific measures such as repeat revascularizations avoided, TLR (target lesion revascularization) and TVR (target vessel revascularization). Furthermore, studies were only included if they reported results in enough detail to enable separation of incremental costs from incremental effects. There was no restriction on the perspective used in the economic evaluation. Reviews, editorials and abstracts were not included in the review.

Studies were identified using electronic databases (PubMed, EMbase, NHS EED, Cochrane Library and INAHTA) and by scanning reference lists of eligible articles. The full search strategies for EMbase and PubMed are presented in appendix 6.1. To ensure that all relevant publications were identified in the CRD (NHS EED and HTA) and Cochrane Library databases we limited the search terms to “stent” and “stents”. These terms were searched in “any field” for CRD and in “title, abstract, keywords” for Cochrane Library. We also included the relevant publications found in the reviews by Ligthart et al.[121], Hill et al.[91], and Neyt et al.[120].

Data extraction

One reviewer (LB) screened the titles and abstracts identified through the searches. The full text evaluation was performed by two reviewers (LB & FW) and discrepancies were discussed and resolved by consensus or by consulting a third reviewer (WR). Various parameters (Tables 6.1 and 6.3) were extracted from the relevant publications by one reviewer (LB). Costs were converted to Euros[47] and corrected for inflation if necessary[48] to present the costs as 2012 Euros. In addition, two reviewers (LB & FW) independently assessed the quality of the models using the Philips et al. checklist[122] for the assessment of model-based economic analyses. The Philips checklist is a framework based on existing guidelines on the use of decision analytic modelling in health technology assessments. The checklist is structured in three themes: a) structure, which focusses on the scope and mathematical structure; b) data, which examines data identification and uncertainty methods; and c) consistency, which assesses the overall quality of the model based on the publication. Both overall study quality and the quality per theme were given a score from 0–100%, which was calculated by dividing the sum of the questions answered positively by the total number of relevant questions. Since some questions were not relevant for all studies (e.g. questions concerning quality-of-life values) the denominator could differ between studies.

Analysis

The influence of modelling methods, the choice of parameters and the quality of the models on the main outcomes (incremental costs, incremental QALYs and absolute risk reduction repeat revascularizations) were analysed both quantitatively and qualitatively. Associations between parameters and the outcomes were assessed by identifying outliers found on cost-effectiveness planes. Furthermore, several bivariate linear regressions were estimated to confirm the associations and also to measure the influence of other parameters on the outcomes. Including associations that could be predicted beforehand (e.g. type of lesion, price stent) are included in the regression analyses since it could be seen as a validation check if the model predicts what it should predict.

We included every subgroup or sensitivity analysis found in a study as long as incremental costs or incremental effectiveness were provided or could be calculated. As a result, our meta-regression analyses were based on many more observations than the number of studies that were included. Since Hill et al.[91] provided more than 30% of the observations used in our study; we incorporated study ID as a random effect in the regression models. Data management and all statistical analyses were performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Figure 6.1 presents the process of identifying relevant publications. Of the 1957 potentially relevant publications, 1872 were excluded based on title, abstract and keywords. Full-text evaluation was performed for 85 articles leading to 18 relevant studies. Reasons to exclude studies after a full text assessment were: lack of a model (n=24), no original CEA (n=22), language other than English (n=8), no relevant outcome (n=6), comparator not BMS (n=4), and results were not presented at a disaggregated level (n=3). In one case, we found that a full report[123] and a paper[101] reported results from the same analyses; data was therefore extracted from the full report. In another case, we found two papers with the same content and results and considered them as one paper[124,125].

The 16 eligible studies were divided into five groups based on the type of DES that was evaluated and accounted for 508 separate analyses (Table 6.1). Four studies calculated the incremental cost-effectiveness ratio (ICER) for both PES and SES[91,92,99,126], two studies[93,127] focused on PES, three studies focused only on SES[98,128,129], and one study used ZES as the intervention[97]. The remaining six publications[90,94-96,123-125] did not specifically identify the type of eluting drug under evaluation and calculated an ICER for a DES in general.

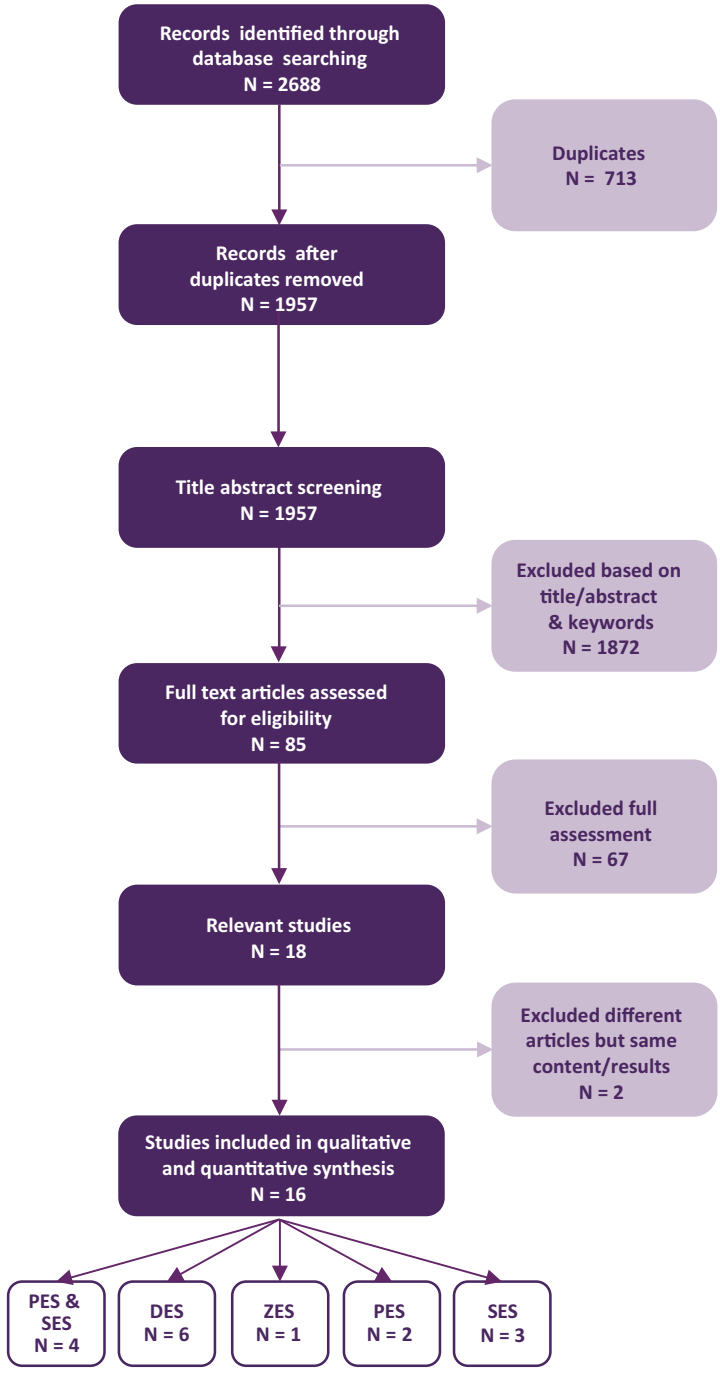

Figure 6.1 | Flow of studies through the review process

PES: paclitaxel eluting stent; SES: sirolimus eluting stent; ZES: zotarolimus eluting stent; DES: drug eluting stent

Descriptive characteristics

In most analyses, DES was more expensive (88% of analyses) and more effective in both QALYs and repeat revascularizations avoided (99% of analyses) than BMS. Most of the 16 studies[91,92,95,96,123-125,127] concluded that DES is not cost-effective for all subgroups since the incremental QALYs did not offset the incremental costs. However, many concluded that DES was more cost-effective in high-risk patients. The ICER varied considerably between and within studies: from DES being dominated by BMS[92,95] to DES being dominant in specific analyses[90,91,93,123-125,129]. Figures 6.2 and 6.3 present the variability of the incremental costs and effects of the studies using repeat revascularizations avoided or QALYs as an outcome measure, respectively. The mean values of input parameters stratified by the type of study outcome are presented in Table 6.2.

We also assessed the quality of the models of all studies using the Philips et al.[122] checklist. Studies appeared to score higher on the theme structure (63%±16%) than on the other two themes, data (55%±21%) and consistency (59%±21%). The overall quality of the models was moderate (mean 59%±15% of a maximum possible score of 100%).

Outcome repeat revascularizations avoided

Based on 124 separate analyses (9 studies), the number of repeat revascularizations avoided (the absolute risk reduction in repeat revascularizations) with DES also varied considerably (Figure 6.2) between and within studies (range: -0.0001, 0.19), which resulted in variation in the ICERs. The overall conclusions of most of the studies corresponded with the 124 separate analyses. The regression analyses showed that the relative risk reduction of repeat revascularizations and the initial probabilities of restenosis were positively associated with repeat revascularizations avoided. Furthermore, a more complex vessel or lesion was associated with higher relative risk reduction and initial risk of restenosis after a percutaneous coronary intervention with BMS. Consequently, this leads to an increase in repeat revascularizations avoided and DES becomes more effective. Furthermore, the number of stents was also positively and significantly associated with repeat revascularizations avoided, probably because it is a proxy for subgroups who have a higher risk of developing restenosis due to diabetes, lesions and vessels characteristics.

Besides these factors that could be predicted beforehand, with the meta-regression analyses we were able to find a negative association between overall quality of a model and repeat revascularizations avoided. Furthermore, the theme consistency was also negatively associated with this incremental outcome. Consequently, models with a higher quality led to less favourable results for DES.

Table 6.1 | Description economic evaluations

Study	Year	Country	# Analyses	Horizon (months)	Model	Funding†	Subgroups	Comparison	Price per stent	Price difference DES vs BMS	# Stents per procedure	Quality (%)*
Ekman et al.[93]	2004	Sweden	66	12,24	DT	Yes	High risk, diabetes, type of lesion, type of vessel	BMS vs PES	NS NS	 €693–€1,271	1.1–1.8	41
Hill et al.[90]	2004	UK	36	12-60	STM	No	High risk, # vessels	BMS vs DES	€679 €1,607	 €929	1.3,2.4	77
Tarricone et al.[129]	2004	Italy	10	12	DT	Yes	# vessels, diabetes, type of lesion, type of vessel	BMS vs SES	NS NS	 €0	1.2-2.6	46
Bowen et al.[95]	2005	Canada	50	12	DT	No	Post MI, diabetes, type of lesion	BMS vs DES	€531 €1,681	 €1,150	1.23–2.26	61
Mittmann et al.[126]	2005	Canada	8	12	DT	NS		BMS vs SES PES	€522 €2,062 €2,062	 €1,540 €1,540	1.5	50
Shrive et al.[98]	2005	Canada	11	LT	STM	Yes	Diabetes, age	BMS vs SES	€430 €1,246–€3,114	 €816–€2,685	1.05–1.75	56
Mahieu et al.[99]	2006	Belgium	31	12	DT	NS	Diabetes, type of lesion, type of vessel	BMS vs SES PES	NS NS NS	 €731–€1,306 €731–€1,306	1	32
Hill et al.[91]	2007	UK	172	12	STM	No	High risk, elective	BMS vs SES PES	€485 €1,700–€1,774 €1,621–€1,696	 €1,215–€1,289 €1,136–€1,211	1–2	80
Kuukasjarvi et al.[96]	2007	Finland	2	24	DT	No		BMS vs DES	NS NS	 NS	NS	33
Neyt et al.[123]	2007	Belgium	59	12	DT	NS	Diabetes, # vessels, type of lesion	BMS vs DES	€553–€1,106 €553–€1,659	€0–€1,106	1.09–1.97	72
Polanczyk et al.[128]	2007	Brazil	4	12, LT	STM	Yes		BMS vs SES	€831–€1,390 €3,169	 €1,779, €2,337	1.2	56

Table 6.1 | *(Continued)*

Study	Year	Country	# Analyses	Horizon (months)	Model	Funding†	Subgroups	Compari-son	Price per stent	Price difference DES vs BMS	# Stents per procedure	Quality (%)*
Bischof et al.[92]	2009	USA	4	36	STM	No		BMS vs SES PES	NS NS NS	NS	NS	76
Goeree et al.[94]	2009	Canada	45	24	DT	No	Diabetes, type of lesion, type of vessel	BMS vs DES	€470 €1,486	€391–€1,016	1.1–2.37	52
Ferreira et al.[127]	2010	Brazil	1	26	DT	No		BMS vs PES	€1,883 €5,272	€3,390	NS	36
Jahn et al.[124,125]	2010	Austria	6	84	DESM	No	Diabetes, type of lesion	BMS vs DES	NS NS	NS	1.24	47
Remak et al.[97]	2010	UK	3	48	STM	Yes		BMS vs ZES	€4,33 €1,175	€742	1.11 1.12–1.4	62

* Philips checklist 2006: scale 0–100%

† Yes: manufacturer; No: funded by government or not funded

LT: life time; vs: versus; DT: decision tree; STM: state-transition model; DESM: discrete event simulation; # vessels: number of vessels treated; MI: myocardial infarction

Outcome of incremental QALYs

Figure 6.3 presents the incremental QALYs and incremental costs for 384 separate cost-effectiveness analyses (11 studies). This Figure shows that Shrive et al.[98] and Remak et al.[97] clearly found a larger incremental QALY gain than the other studies.

Again the meta-regression analyses found associations with incremental QALYs that were expected. Relative risk reduction of repeat revascularizations and the initial probability of restenosis after BMS were associated with a greater QALY gain, as seen in individual sensitivity analyses[90-95].

Table 6.2 | Averages economic evaluations (univariate analyses)

	Total (CEAs & CUAs)	CEAs	CUAs
	Average ± SD	**Average ± SD**	**Average ± SD**
Input parameters			
Number of stents per procedure	1.503 ± 0.367	1.382 ± 0.355	1.540 ± 0.364
Price of DES stent	€1,654 ± €390	€1,912 ± €672	€1,614 ± €307
Price of BMS stent	€555 ± €166	€670 ± €307	€534 ± €114
Price difference between stents	€1,085 ± €337	€1,189 ± € 336	€1,056 ± €331
Price of DES procedure (incl. stents)	€6,328 ± €2,509	€7,811 ± €1,475	€5,998 ± €2,573
Price of BMS procedure (incl. stents)	€4,442 ± €2,195	€6,259 ± €1,536	€4,160 ± €2,138
Cost difference between the procedures	€1,787 ± €686	€1,551 ± €805	€1,840 ± €647
Probability restenosis BMS	0.142 ± 0.076	0.148 ± 0.055	0.140 ± 0.081
Probability restenosis DES	0.064 ± 0.038	0.056 ± 0.027	0.068 ± 0.041
Relative risk reduction DES vs. BMS	0.484 ± 0.204	0.578 ± 0.214	0.449 ± 0.189
Quality (0–100%)*			
Total	59.5 ± 15.4		
Structure	62.5 ± 16.1		
Data	56.7 ± 21.6		
Consistency	55.1 ± 20.8		

* N=16 studies
CEA: cost-effectiveness analysis; CUA: cost-utility analysis

Furthermore, analyses showed that non-elective patients, patients with a high risk of a repeat revascularization, patients with complex vessels or lesions or older patients will benefit more from DES, what was also recognised in the individual studies[91,94,95,98,99]. In addition, we found a significant positive association between time horizon (continuous) and incremental QALYs. This was also found by Hill et al.[90], who varied the time horizon from 12 to 60 months in the sensitivity analyses.

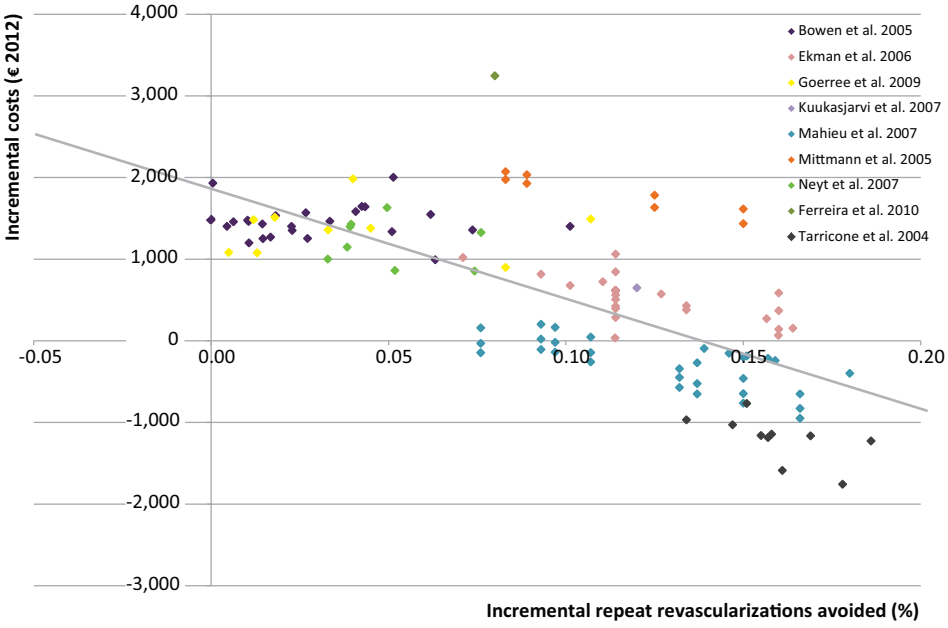

Figure 6.2 | Cost-effectiveness plane, repeat revascularizations avoided

Studies[91,98] that have explicitly mentioned that they have assumed that the occurrence of repeat revascularizations within the time horizon is the result of restenosis and studies assuming that repeat revascularization rates are based on angiographic follow-up have estimated significantly higher incremental QALYs. Angiographic follow-up leads to inflated estimates of clinical effectiveness compared with clinical follow-up since not clinically significant restenosis results in "unnecessary" repeat revascularizations when angiographic follow-up is performed. Consequently, the difference in repeat revascularizations will be overestimated (oculo-stenotic effect)[130]. Some studies use "real-world"[95,123-125] follow-up data and consequently report lower estimates (visible in Figures 6.2 and 6.3) than other studies such as, Remak et al.[97] that used angiographic follow-up[93,96,98,99]. This phenomenon is described earlier by Eisenberg et al.[131], who concluded that cost-effectiveness studies using angiographic follow-up overestimate the cost-effectiveness of DES.

The meta-regression analyses showed that studies using real-world evidence compared with angiographic follow-up leads to a reduction in incremental QALY gain. The added value of meta-regression analyses is limited in explaining the variation in incremental QALYs, however it identified modelling assumptions that were significantly associated.

Outcome incremental costs

Figures 6.2 and 6.3 show that there was large variation in incremental costs (range: €-4,070 to €3,506). Regression analyses confirmed associations (cost parameters and population characteristics) that were seen in the individual studies[91,94,95,97-99,123]. The analyses showed that probability of restenosis after BMS, the reduction in restenosis risk by DES, the difference in stent price, and the number of stents used were important parameters influencing the incremental costs. Both input parameters varied considerably between the analyses: the difference in stent costs ranged from €0[123] to €2,685[98] and the number of stents varied between 1 and 2.6 stents per procedure depending on the type of patient.

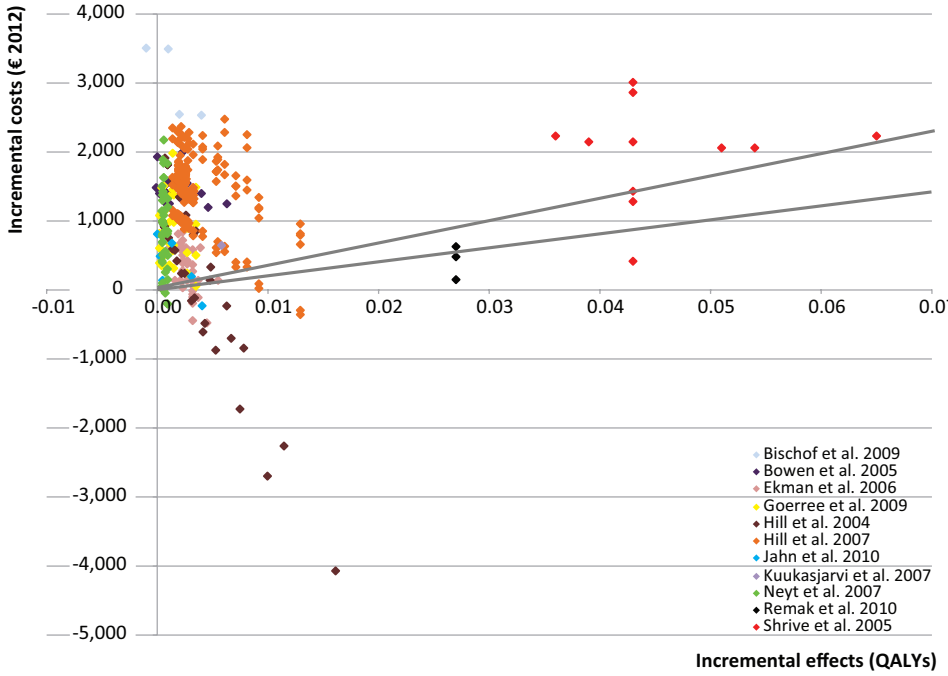

Figure 6.3 | Cost-effectiveness plane, quality adjusted life years

On a meta-level we were able to conclude that funding and the type of cost-effectiveness analysis was associated with incremental costs. Funding was provided by the stent manufacturer in five[93,97,98,128,129] of the 16 studies and three of them[93,97,129] concluded that DES was cost-effective compared with BMS. Of the studies that were not funded by a manufacturer only one[124,125] of them concluded that DES could be cost-saving. Studies that were not funded estimated on average higher incremental costs than studies that were ($p<0.05$). Furthermore, some associations with

incremental costs are recognised from scenario analyses performed by studies. The directions of the following associations are confirmed by the regression analysis but not significant. According to Jahn et al.[124,125] it is important to incorporate wait time into the model since it leads to a decrease in incremental costs. A time horizon shorter than 12 months was associated with higher incremental costs; Hill et al.[90] estimated costs and effects for different time horizons and showed that a longer time horizon led to lower incremental costs. This is likely because of the continuing treatment effect of DES in the subsequent years which would increase in the number of repeat revascularizations avoided compared with BMS. This increase in reduction of repeat revascularization would further offset the cost of the initially more expensive DES.

Meta-regression analyses showed also that the number of repeated revascularizations avoided explained a large proportion of variation (R^2=0.53). As shown in Figure 6.2, there appeared to be a linear association between incremental costs and repeat revascularizations avoided. Incremental QALYs (Figure 6.3), on the other hand, was not associated with incremental costs (R^2=0.001), probably since incremental QALYs are determined by several factors including repeat revascularizations avoided, life-years gained and quality of life values.

DISCUSSION

This study has explored the usefulness of meta-regression analyses in combination with a systematic review of economic evaluations. The variation in incremental costs and effects of studies evaluating the cost-effectiveness of DES versus BMS was explained by using this method. Besides confirming associations that could be predicted based on individual studies, we were able to identify associations on a meta-level such as the quality of the models. Using regression analyses to explore the associations between the incremental outcomes and parameters is unique for a systematic review of economic evaluations.

The most important factors that were associated with the results were patient characteristics (age, vessel, lesion), procedure (type of stent and elective versus non-elective), specific input parameters (number of stents per procedure, cost per stent/procedure, restenosis risk with BMS and the efficacy of DES) and the quality of the models. Many of these associations had already been reported in the studies themselves, which can be seen as evidence that the meta-regression produced valid results. However, besides these previously reported associations, we also found associations between study outcomes and the quality of the model, time horizon, efficacy assumptions, and funding which could only be identified at a 'meta level'. Moreover, this review showed that it is possible to predict the incremental costs based on the absolute risk reduction in repeat revascularizations on 'meta-level' (Figure 6.2).

Table 6.3 | Associations between outcomes and covariates (bivariate analyses)[a]

Covariates	Bivariate		
	Outcomes		
	Δ Costs	Δ QALYs	Δ Repeat revascularization
	β	β	β
Population			
Age			
Age >75	315	0.029*	NA
Age 65–75	-31	0.015*	-0.018
Age <65	ref	ref	ref
Complex lesion (yes vs. no)	181*	0.001*	0.029*
Complex vessel (yes vs. no)	-22	0.001*	0.042*
Multi vessel disease (yes vs. no)	149	0.001	0.019*
Diabetes (yes vs. no)	-216*	0.000	0.02*
Post MI (yes vs. no)	-88	0.000	0.007
Elective (yes vs. no)	346*	-0.001*	NA
High risk (yes vs. no)	-291	0.004*	NA
Intervention			
Type DES			
Sirolimus eluting stent	551	0.01	0.102*
Paclitaxel eluting stent	379	0.011	0.063*
Zotarolimus eluting stent	-324	0.025	NA
Drug eluting stent in general	ref	ref	ref
Study characteristics			
Horizon >1 year (yes vs. no)	-479	0.002	-0.006
Horizon (months) [b]	-32*	0.000*	0.000
Type of study (CUA vs. CEA)	-194*	NA	NA
Model			
Markov model	613	0.014	NA
Discrete event simulation model	-435	0.001	NA
Decision tree	ref	ref	NA
Perspective			
Health care provider perspective	266	0.006	0.004
Health care sector perspective	-1,332	NA	0.04
Non-public perspective	-1,057	NA	NA
Health care payer perspective	ref	ref	ref

Table 6.3 | *(Continued)*[a]

Covariates	Bivariate		
	Outcomes		
	Δ Costs	Δ QALYs	Δ Repeat revascularization
	β	β	β
Funding			
No	1,350*	-0.001	0.03
Yes			
Both Industry and No industry	1,246	0.043*	NA
Industry	-621	0.012	0.102*
No industry	ref	ref	ref
Discounting (yes vs. no)	929	0.016	-0.063
Input parameters			
Number of stents used during the procedure	708*	0.001	0.033*
Price difference between stents	1,215*	NA	NA
Price of BMS stent	0.503*	NA	NA
Price of DES stent	1,001*	NA	NA
Costs of BMS procedure (incl. stents)	0.339*	NA	NA
Costs of DES procedure (incl. stents)	0.412*	NA	NA
Difference in procedure costs	0.799*	NA	NA
Probability of restenosis BMS	-3,072*	0.024*	0.521*
Probability of restenosis DES	-1,907*	0.005	0.436*
Relative risk reduction repeat revascularization	-1,676*	0.007*	0.132*
Disutility of undergoing a CABG	NA	-0.107	NA
Disutility of undergoing a PCI	NA	-0.747*	NA
Disutility of experiencing a MI	NA	-0.021	NA
Disutility for a patient with angina symptoms	NA	-0.012	NA
Quality of life of a patient with angina symptoms	NA	-0.231*	NA
Quality of life of a patient after revascularization (recovered)	NA	-0.24*	NA
Quality of life of a patient suffering from restenosis	NA	-0.254*	NA
Assumptions			
Difference in clopidogrel (medication) usage (yes vs. no)	181	0.00*	0.001
Wait time for revascularization included (yes vs. no)	-733	-0.012*	-0.051
Repeat revascularization is based on angiographic follow-up data (yes vs. no)	-593	0.013*	-0.082*
DES and BMS are not mixed up during a procedure	-541	0.002	-0.061
Repeat interventions that occur during time horizon are the result of restenosis	854	0.02*	NA

Table 6.3 – *(Continued)*[a]

Covariates	Bivariate Outcomes		
	Δ Costs	Δ QALYs	Δ Repeat revascularization
	β	β	β
The type of repeat revascularization is the same for the DES and BMS treatment groups	501	-0.008	-0.071
There does not exist a difference in survival between DES and BMS	-238	0.001	0.015
There does not exist a difference in thrombosis between DES and BMS	-589	-0.003	0.039
There does not exist a difference in MI between DES and BMS	-594	-0.006	0.046
Quality of studies (Philips et al. 2006)[122]			
Structure (%)	2,154	-0.006	-0.145
Data (%)	1,607	0.006	-0.167*
Consistency (%)	718	-0.018	-0.153
Total (%)	2,761	0.000	-0.250*

[a] Corrected for study; [b]Shrive et al. & Remak et al.[97,98] not included (lifetime horizon)
* p value<0.05

Some of the associations we found are desirable since they involve parameters that influence the results and that can be controlled by clinicians and policymakers. For example, factors like the costs of a stent are expected to be associated with the results. Other factors such as patient characteristics can be changed by means of patient selection. However, the presence of other associations such as the quality of the models, assumptions, time horizon or funding raises concerns. Moreover, other parameters were not significantly associated but also these differences are undesirable and could have influenced the outcomes. It is important for authors to follow the recommendations of the ISPOR-SMDM task force for modelling good research[132] to increase the quality of the study and generalizability of the results.

Limitations

Despite the fact that the quality of models was assessed by two independent reviewers it was difficult to judge the quality due to subjectivity of the questions; this problem was been recognized in the past[133]. Furthermore, to provide studies with a score between 0 and 100% we needed to assume that all questions of the checklist were equally important. Thus studies could obtain a reasonably high score if less informative/important questions were fulfilled. In addition, the quality of the models was based on the documentation of the model and therefore it is

possible that studies that scored low did not transparently present model details, however the actual model could be of high quality.

Another limitation of our study is that all 508 analyses were analysed as independent observations even though in reality these 508 analyses were based on 16 studies. We have used study identification number as a random effect in the regression models to address this problem. In addition, transparency in documentation is a major issue leading to a high frequency of missing values that made it impossible to perform multivariate analyses with all of the parameters that were significant in the bivariate analyses. Transparent reporting is crucial in this field and would solve the problem of missing values for systematic reviews such as this. A recently published review on the challenges of modelling the cost-effectiveness of cardiovascular disease interventions has recognized the same problem[134].

Lastly, we did not include the studies published after January 2012. However, we expect that including newer studies that met inclusion criteria (i.e. estimating the cost-effectiveness of DES versus BMS using modelling methods) do not have an impact on the results of our case study showing that using meta-regression analyses could be useful method in addition to conventional systematic reviews.

Conclusions

This study has showed that meta-regression analyses can be of added value, identifying significant associations that could not be identified using conventional review methods or sensitivity analyses of individual studies. The quality of the models was associated with the outcomes of the studies and therefore it is important that a quality check is performed before interpreting the results of the study.

Appendix 6.1 – Search terms

Pubmed	
#1	cardiovascular disease[MeSH]
#2	stent*
#3	economics
#4	econom*
#5	cost
#6	costs
#7	costly
#8	costing
#9	price
#10	prices
#11	pricing
#12	pharmacoeconomics
#13	pharmacoecon*
#14	expenditure*
#15	energy
#16	#13 NOT #14
#17	“value for money”
#18	budget*
#19	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #15 OR #16 or #17 OR #18
#20	Humans[Mesh]
#21	“1990”[PDat] : “2012”[PDat]
#22	English[lang]
#23	#1 AND #2 AND #19 AND #20 AND #21 AND #22

Appendix 6.1 – Search terms

Embase	
#1	'cardiovascular disease'/exp
#2	'stent'/exp
#3	'economics'/exp
#4	'cost'/exp
#5	costly
#6	costing
#7	price
#8	prices
#9	pricing
#10	pharmacoeconomics
#11	'pharmacoeconomics'/exp
#12	'value for money'
#13	'budget'/exp
#14	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	[humans]/lim
#16	[1-1-1990]/sd NOT [31-12-2011]/sd
#17	[english]/lim
#18	#1 AND #2 AND #14 AND #15 AND #16 AND #17

Cochrane (43) CRD (205) and INAHTA (24) are checked for relevant publications
Economic filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter [Internet]. York: Centre for Reviews and Dissemination; 2010. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html


Challenges
Modelling
Cardiovascular
Technologies
Tests
Devices
QALY
ICER
Analyses
Markov
Cost-effectiveness
Disease
Costs
Data
Blood
Results
Extrapolating
CVD
Thesis
PCI
CAD
Intervention
Diagnosis
Prevention
Follow-up
Drugs
Scenario Analyses
Sensitivity Analyses
Specificity
Angina
Guidelines
TAVI
EVAR
RCT
Stroke
Literature
Efficacy
Precision
Structure
Bias
Validity
Outcomes
Survival
Statin
Accuracy
CT-scanner
Persistence
Identification
Frequency
Interaction
Decision Tree
Prior Likelihood
ICA
Gold Standard
False Negative
False Positive
True Negative
Risks

Chapter 7

The cost-effectiveness of elective endovascular aneurysm repair versus open surgical repair of abdominal aortic aneurysms

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Submitted

ABSTRACT

Background: Patients diagnosed with a large unruptured abdominal aortic aneurysm (AAA) are usually offered elective reparative treatment given the high risk of rupture. Nowadays, patients with an AAA diameter larger than 5.5cm are treated with open surgical repair (OSR) or endovascular aneurysm repair (EVAR). The aim of this study is to estimate the lifetime cost-effectiveness of EVAR versus OSR in the Netherlands based on recently published literature.

Methods: A model was developed to simulate a cohort of individuals (72 years old, 87% men) with a diagnosed AAA diameter of at least 5.5cm and considered fit for both repairs. The model consists of two submodels that estimate the lifetime cost-effectiveness of EVAR versus OSR: 1) a decision tree for the first 30 days post-operative and 2) a Markov model for the period thereafter (beyond 30 days to 30 years).

Results: In the base-case analysis, EVAR was slightly more effective (4.704 versus 4.669 QALYs) and less expensive (€24,483 vs. €25,595) than OSR. Improved effectiveness occurs because EVAR can reduce 30-day mortality risk as well as the risk of events following the procedure while lower costs are primarily due to a reduction in hospital days. The cost-effectiveness of EVAR is highly dependent on the price of the EVAR device and the reduction in hospital days, complications and 30-day mortality.

Conclusion: EVAR and OSR can be considered equally effective, while EVAR can be cost-saving compared with OSR. EVAR can therefore be considered a cost-effective solution for AAA patients.

INTRODUCTION

Patients diagnosed with a large unruptured abdominal aortic aneurysm (AAA) are usually offered elective operative repair given the high risk of rupture. Nowadays, patients with an AAA diameter larger than 5.5cm[135] are treated electively with open surgical repair (OSR) or endovascular aneurysm repair (EVAR). Several randomized controlled trials (RCT) such as the DREAM[136], EVAR-1[137], OVER[138] or ACE[139] trials have compared the effectiveness of EVAR versus OSR and concluded that EVAR leads to a reduction in short term mortality. A systematic review by Chambers et al.[140] showed that EVAR may significantly decrease 30-day mortality and 6-month all-cause mortality primarily due to a lower mortality rate during initial hospitalisation[141]. However, EVAR seems to increase the four year chance of AAA-related reinterventions (9%) compared with OSR (1.7%)[142] and RCTs showed that the gain in all-cause mortality disappears after the first 2 years[143].

The various observed differences in effectiveness between EVAR and OSR underline the need to compare the two procedures in a comprehensive manner. Moreover, costs need to be considered as well, since the device used in an EVAR procedure is more expensive than the prosthesis used for OSR. These are two important reasons to examine cost-effectiveness of EVAR versus OSR.

Several cost-effectiveness analyses have examined the cost-effectiveness of EVAR versus OSR in different settings[140,143]. A previous study estimated the cost-effectiveness of elective EVAR versus OSR for the Netherlands[144], however the time horizon of the analysis was one year and the data was based on the DREAM trial[136] which started patient inclusion in 2000. In the economic evaluation[144], based on the DREAM trial, they concluded that EVAR was not cost-effective compared with OSR. Other studies have also estimated the cost-effectiveness of EVAR compared with OSR albeit for another setting and often also used results that were slightly outdated and several clinical events were not included. Since endovascular AAA repair is a very dynamic field, its cost-effectiveness should be estimated with recent data, including cost data, technological improvements of the device and the technical skills of clinicians with EVAR. The aim of this study is to estimate the lifetime cost-effectiveness of elective EVAR versus OSR in AAA patients in the Netherlands, from a societal perspective.

METHODS

A model was developed to simulate a cohort of individuals (72 years old, 87% men[145]) with a newly diagnosed AAA of at least 5.5cm in diameter and were considered fit for elective OSR and EVAR.

The model estimates the lifetime cost-effectiveness of elective EVAR versus OSR. The measure of health benefit was expressed in expected quality adjusted life years (QALYs) and costs were measured in 2013 Euros. A societal perspective, as proposed by the Dutch guidelines[146], was adopted, however indirect costs and non-medical costs were assumed to be equal between the treatment strategies and were left out of the analyses. Costs and health benefits were discounted at 4% and 1.5%, respectively, according to the current Dutch guidelines[146]. The model is closely based on a previously published model[147] but is adjusted in several aspects: 1) costs of procedures are adapted to the Dutch setting, 2) additional events are included (e.g. deep venous thrombosis (DVT), pulmonary embolism (PE), major amputation of lower extremities), 3) transition probabilities (e.g. mortality and events) are derived from other sources presenting more detailed data, 4) quality of life (QoL) values are based on the DREAM trial[144].

Structure

The model consists of two submodels, namely a short term decision tree model (which captures events that take place in the first 30 days post-operative) and a long term Markov model to model disease progression thereafter (up to 30 years). Patients who experienced pre-operative complications while waiting to undergo the operation were not included in this analysis; we assumed no differences in costs and effects between the interventions during waiting time (expert opinion).

Short term model

The short term model (Figure 7.1) includes 30-day mortality, conversion from EVAR to OSR, and events (AAA and laparotomy related reintervention, major amputation of lower extremities, myocardial infarction (MI), DVT, PE, pneumonia, permanent and temporary renal failure, disabling and non-disabling stroke).

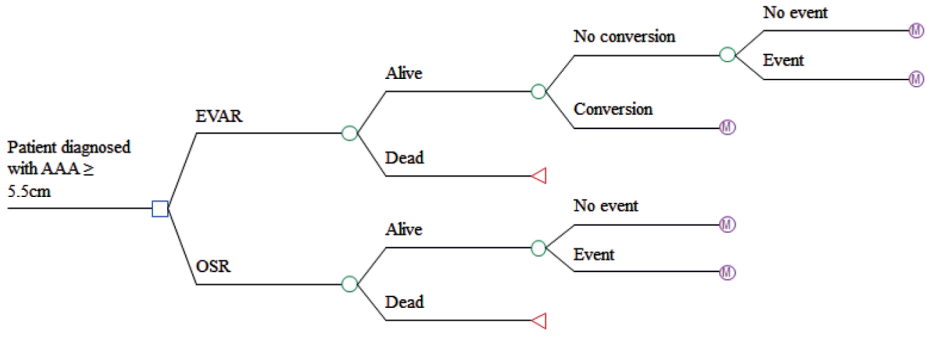

Figure 7.1 | Short term model (first 30 days)

AAA: abdominal aortic aneurysm; EVAR: endovascular aneurysm repair; OSR: open surgical repair

Long term model

The costs and health effects (life-years, QALYs) of patients who survive the first 30 days post procedure are estimated in the long term model (Figure 7.2) for a lifetime horizon (30 years). The cycle length used in the first two years was 1 month and after two years a yearly cycle was used. This model consists of four disease states ('Alive, no event', 'Post non-fatal event - first year', 'Post non-fatal event – subsequent years' and 'Death'). Two 'Post non-fatal event' states were incorporated since the costs and QoL of patients with an event is different for the first year compared to subsequent years[147].

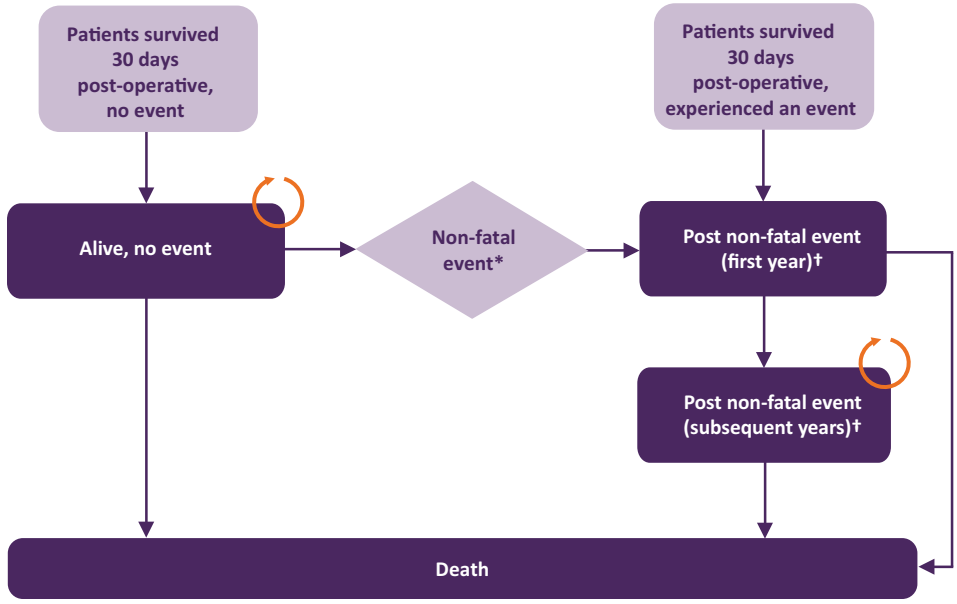

Figure 7.2 | Long term model (beyond 30 days – 30 years)

* Note that non-fatal event is a predicted event and not a state of the model
† These states are heterogeneous; it represents the weighted average of the different types of events

Depending on the occurrence of an event in the first 30 days, patients can enter the long term model in the 'Alive, no event' or in the 'Post non-fatal event - first year' if they have experienced a non-fatal event in the first 30 days. Patients in the 'Alive, no event' state have an ongoing chance of an event (MI or stroke) and an ongoing chance of dying for any reason. Patients who have experienced an event will move to the 'Post non-fatal event – first year' state. The costs and health outcomes of patients that have survived the first year after the event are modelled in the 'Post non-fatal event – subsequent years' state. Patients in the 'Post non-fatal event' states are only at risk of death and not at risk of an additional event. The 'Post non-fatal event' states include patients who have had various types of events, which means that the average costs and QoL

represent weighted averages. The costs and health outcomes of patients who have experienced an event (e.g. stroke, MI, renal failure) are modelled separately in this heterogeneous state. Mortality is not modelled separately, since specific risks after each event were not available.

Table 7.1 | Transition probabilities

	Base case*		Distribution EVAR	Distribution OSR	Source
	EVAR	OSR			
Mortality					
Mortality – 30 days (cum)	0.008	0.033			[142]
Mortality – 1 year (cum)	0.063	0.079			[142]
Mortality – 2 year (cum)	0.119	0.119			[142]
Mortality – 3 year (cum)	0.167	0.167			[142]
Mortality – 4 year (cum)	0.216	0.216			[142]
Mortality – 5 years (cum)	0.267	0.267			[142]
Mortality > 5y	age and gender dependent				[28]
Events (<30 days post-operative)					
Reintervention (excl. conversion)	0.0018	0.0033	Beta (42,22788)	Beta (75,22751)	[148]
Conversion to open surgery	0.0024	-	Beta (3,1253)	-	[149]
MI	0.07	0.093	Beta (1598,21232)	Log-normal (1.340,0.03)†	[142]
DVT or PE	0.011	0.017	Beta (251,22579)	Log-normal (1.210,0.079)†	[142]
Stroke	0.001	0.001			[143]
Disabling	0.309	0.309	Beta (62,139)	Beta (62,139)	[150]
Pneumonia	0.093	0.168	Beta (2123,20707)	Log-normal (1.890,0.026)†	[142]
Community management	0.68	0.68	Beta (68,32)	Beta (68,32)	Assumption[147]
Acute renal failure	0.055	0.107	Beta (1256,21574)	Log-normal (2,0.034)†	[142]
Renal failure requiring dialysis	0.004	0.05	Beta (91,22739)	Log-normal (1.33,0.143)†	[142]
Major amputation	0.0004	0.0012	Beta (9,22821)	Log-normal (3.0,0.365)†	[142]
Proportion above knee	0.317	0.317	Beta (13,28)	Beta (13,28)	[151]
Events (>30 days post-operative) Annual probability					
Reintervention	0.049	0.039	Beta (1126,21700)	Beta (888,21938)	[148]
Cardiovascular event (stroke & MI)	0.026	0.031	Beta (16,610)	Log-normal (1.205,0.146)†	[143]
Proportion MI	0.487	0.487	Beta (55,58)	Beta (55,58)	[143]

* Base case: 72 year old, 87% men †RR was used

Cum: cumulative; DVT: deep venous thrombosis; EVAR: endovascular aneurysm repair; MI: myocardial infarction; OSR: open surgical repair; PE: pulmonary embolism

Input parameters

A literature search using PubMed was performed to obtain values of input parameters and experts were consulted whenever needed. An expert panel of four vascular surgeons [AW (peripheral teaching hospital), PC and AV (large teaching hospital), HV (academic hospital)] provided feedback on structural assumptions, provided cost data and validated the values that were used for the input parameters. Table 7.1 presents the values of the input parameters of the base-case analysis and their distributions used in the uncertainty analyses. Tables 7.2 and 7.3 present the costs (unit costs and resource use) and the QoL values used in the analysis.

Probabilities

Survival

In the base-case analysis, the estimated 30-day all-cause mortality rate and the 5-year post-operative all-cause mortality rate were based on the results of a large cohort study evaluating the effectiveness of EVAR and OSR in a US Medicare population (n=45,660 patients)[142]. Since individual patient data were unavailable, mortality rates were directly derived from the Kaplan-Meier curves published in the article. Mortality rates for OSR and EVAR beyond 5-year follow-up were derived from Dutch national age-and gender-specific mortality statistics[28] by adjusting all-cause mortality with a multiplication factor of 1.36 in men and 1.86 in women[152]. This multiplication factor, based on the UK small aneurysm trial[152], leads to an increase in mortality since patients with AAA have a higher mortality risk than the general population. Mortality rates were independent of the disease state.

Events

The risks of events during the first 30-day post-operative, including circulatory system events (DVT, PE and MI), neurological events (stroke), renal events (renal failure), pulmonary events (pneumonia), were based on Schermerhorn et al.[142] and Brown et al.[143]. In total, patients treated with EVAR had a lower 30-day event rate than patients treated with OSR (24% versus 40% respectively) in the base-case analysis. The reintervention rate was based on Giles et al.[148] (same data as in the Schermerhorn paper). The chance of a conversion from EVAR to OSR was based on the study by Stokmans et al.[149].

The risks of events after 30 days were based on Brown et al.[143], who reported the outcomes of the EVAR-1 trial, while the probabilities of reintervention were based on Giles et al.[148]. Patients treated with EVAR had a higher reintervention rate than the OSR group, mainly because of the higher AAA-related reintervention rate (3.6% versus 0.9%). However, patients treated with OSR had a higher chance of laparotomy related reinterventions (e.g. bowel resection or repair of abdominal-wall hernia) than EVAR patients (2.99% versus 1.38%). These rates were based on six-year follow-up results and were assumed to continue after these six years. Schermerhorn et al.[142] reported four-year follow-up results and showed that the reintervention risk stays fairly constant over the years.

Costs and quality of life

Unit costs and resource use were obtained from hospital databases, the Dutch Surgical Aneurysm Audit (DSAA)[145], literature and expert opinion (Table 7.2). We combined these estimates with reference values from the Dutch costing manual[153] and Dutch tariffs[154].

The costs of the primary admission for EVAR and OSR were based on a large Dutch AAA registry[145] and data obtained from three general hospital databases. These costs include the device and guidewires, theatre time, consumables, blood products, cell saver, diagnostics, laboratory, and length of stay on wards and intensive care. The frequency of outpatient visits and follow-up tests were based on expert opinion. It was assumed that patients who underwent EVAR have an outpatient visit with a diagnostic test (duplex test (80%) or computed tomography (20%)) at one month follow-up and then once every year thereafter. Patients treated with OSR were assumed to have an outpatient visit at one month and six months follow-up, after which they would have an outpatient visit in combination with a computed tomography (50%) or a duplex test (50%) every five years. Follow-up schedule was based on primary treatment; i.e. reinterventions did not alter the follow-up scheme in the model. Costs of events, reinterventions and conversions were based on previously published studies[37,150,155-160] and inflated and converted to 2013 Euros[47,48].

Total QALYs were estimated by combining QoL values from the DREAM trial[144] with UK population norms[71] and survival. The DREAM trial[136] is the only randomised trial that measured QoL, using the EQ-5D, in Dutch patients undergoing EVAR or OSR who were considered fit for both procedures. EVAR patients had a higher QoL than OSR patients at 1-month follow-up (0.67 versus 0.61) but a lower QoL at 3 months (0.75 versus 0.78) and 12 months (0.77 versus 0.81). In line with QoL measured in the EVAR-1 trial[137], other studies[161,162], and expert opinion we assumed that QoL is comparable for both groups in the mid-term. In the base-case analysis, we assumed that the QoL of the patient groups did not differ after 18 months and was estimated using the average QoL of both groups at 12 months (0.79). The QoL values of patients experiencing a clinical event were based on several sources[150,151,163,164]. QoL values of patients without experiencing events were estimated by combining population-based QoL with procedure-related QoL. Similarly, the QoL values of patients who have experienced an event were estimated by combining population-based QoL, procedure-related quality of life and event specific QoL.

Analysis

The costs and effectiveness expressed in LY and QALYs were estimated separately for both procedures. Dividing the incremental costs by the incremental effects leads to a deterministic estimate of the incremental cost-effectiveness ratio (ICER) of EVAR versus OSR. This point estimate was estimated when the mean values of the parameters are used (base case). When a strategy is considered more effective and less expensive than the alternative, this strategy is considered dominant and no ICER is estimated.

Table 7.2 | Costs of AAA procedures

	EVAR			OSR			Δ	Sources*
	Resource use	Unit costs	Costs	Resource use	Unit costs	Costs		
Procedure								
Theatre time (hours)	146	€12	€1,813	228	€12	€2,831	-€1,018	[165]; expert opinion
Hospital stay (days)								
Ward	3.7	€498	€1,842	8.8	€498	€4,366	-€2,524	[165;153]
Intensive care	0.27	€2,377	€642	2.7	€2,377	€6,417	-€5,776	[165;153]
Blood (red blood cell units)	0.2	€219	€44	2.1	€219	€460	-€416	[139;153]
Cell saver	0	€198	€0	1	€198	€198	-€198	[166]
Diagnostics			€1,373			€476	*€897*	Unpublished study
Device			€8,000			€627	*€7373*	Expert opinion
Guidewires			€700			€0	*€700*	Expert opinion
Consumables			€109			€177	-€68	Unpublished study
Laboratory			€119			€516	-€397	Unpublished study
Other			€48			€332	-€284	Unpublished study
			€14,690			€16,399	-€1,709	

* Source of resource use; source of unit costs

AAA: abdominal aneurysm repair; EVAR: endovascular aneurysm repair; OSR: open surgical repair

Table 7.3 | Quality of life

Intervention related quality of life	EVAR	OSR	Distribution EVAR	Distribution OSR	Source
1 months	0.67	0.61	Beta (52,26)	Beta (46,29)	[144]
2 months	0.73	0.74	Beta (57,21)	Beta (55,20)	[144]
3 months	0.75	0.78	Beta (58,20)	Beta (59,16)	[144]
6 months	0.75	0.79	Beta (58,20)	Beta (59,16)	[144]
12 months	0.77	0.81	Beta (60,18)	Beta (61,14)	[144]
18 months	0.79	0.79			Assumption[147]
Quality of life complications	**Mean**		**Distribution**		
First year after event					
Major amputation above knee	0.20		Normal (0.2,0.22)		[151]
Major amputation below knee	0.61		Normal (0.61,0.2)		[151]
MI	0.68		Beta (152,70)		[150]
DVT or PE	0.75		Beta (54,18)		[162]
Acute renal failure	0.44		Beta (184,232)		[164]
Renal failure requiring dialysis	0.44		Beta (184,232)		[164]
Pneumonia – community	0.90		Beta (180,20)		Assumption[147]
Pneumonia – hospital	0.85		Beta (170,30)		Assumption[147]
Stroke – disabling	0.38		Beta (56,91)		[150]
Stroke – non-disabling	0.74		Beta (109,38)		[150]
Subsequent years					
Major amputation above knee	0.20		Normal (0.2,0.22)		[151]
Major amputation below knee	0.61		Normal (0.61,0.2)		[151]
MI	0.72		Beta (159,62)		[150]
DVT or PE	0.75		Beta (54,18)		[162]
Acute renal failure	1.00		Beta (200,0)		Assumption[147]
Renal failure requiring dialysis	0.44		Beta (184,232)		[164]
Pneumonia – community	1.00		Beta (200,0)		Assumption[147]
Pneumonia – hospital	1.00		Beta (200,0)		Assumption[147]
Stroke – disabling	0.38		Beta (56,91)		[150]
Stroke – non-disabling	0.74		Beta (109,38)		[150]
Population norms UK	**Mean**		**Distribution**		
Age 65–74	0.78		Beta (361,107)		[71]
Age 75+	0.73		Beta (229,85)		[71]

DVT: deep venous thrombosis; EVAR: endovascular aneurysm repair; MI: myocardial infarction; PE: pulmonary embolism; OSR: open surgical repair

Univariate analyses and scenario analyses were performed to estimate the impact of varying input parameters and assumptions. A scenario analysis was performed to estimate the impact of

the procedure related QoL estimates. The time until the EVAR-treated and OSR-treated patients have the same QoL was varied from 18 months to 24 months and 36 months. Furthermore, an analysis using QoL estimates from the EVAR-1 trial was also performed. An alternative scenario was analysed to estimate the impact of survival modelling methods on the cost-effectiveness of EVAR. Instead of using survival based on Schermerhorn et al.[142], all-cause mortality (4 year) was based on the EVAR-1 trial[143]. Mortality rates for OSR and EVAR beyond 4-year follow-up were modelled as in the base-case analysis using adjusted Dutch national age-and gender-specific mortality statistics[28]. In addition, the cost-effectiveness of EVAR is estimated for a 65 year old patient and an 80 year old patient.

Furthermore, probabilistic sensitivity analyses (PSA) were performed by running a Monte Carlo simulation of 10,000 simulations of the model. In the PSA, parameters were varied simultaneously using a priori defined distribution (Tables 7.1 and 7.3). Gamma distributions were used for costs, log-normal distributions for relative risks, beta distributions were used for utility values and probabilities. In addition, a cost-effectiveness acceptability curve (CEAC) was created to present the probability of EVAR being cost-effective at varying willingness-to-pay thresholds[167].

RESULTS

Base-case analysis

Over a lifetime period, EVAR resulted in more life-years (8.674 LYs versus 8.648 LYs) and QALYs than OSR (4.704 QALYs versus 4.669 QALYs) (Table 7.4). These differences primarily occurred because EVAR patients (99.2%) had a higher 30-day survival compared with OSR patients (96.7%). After that period, the difference in survival diminished ('survival catch-up') and patients had a survival of 88% after 23 months, independent of the treatment they received. Consequently, EVAR patients do not gain any additional life-years after 23 months.

In the DREAM trial, used as the source of QoL values in the base-case analysis, EVAR patients had a higher QoL in the first 2 months than OSR patients, but a lower QoL from 2 months to 18 months follow-up. After that, no difference in procedure-related QoL was seen between the two treatment groups. However, OSR patients have a higher chance of having clinical events (e.g. MI, stroke) which leads to a reduced QoL and fewer QALYs compared to EVAR patients. When QoL values are combined with survival, there is a small QALY gain of 0.017 after one year, which first decreases to 0.013 after two years and then increases slightly to 0.035 over a lifetime.

Over a lifetime period, EVAR resulted in lower costs than OSR (€24,483 versus €25,595) mainly due to the lower initial hospital admission (including procedure) costs. Patients treated with EVAR were admitted to the hospital for 3.97 days, including 0.27 days on an intensive care unit

(ICU), compared with OSR patients who were admitted for 11.5 days, including 2.7 ICU days. The device used in an EVAR procedure (€8,000) is more expensive than the device used in an OSR procedure (€627) but this difference was offset by the reduction in hospital days. Over the years, EVAR became less cost-saving since EVAR patients require more intensive follow-up than OSR patients, leading to an increase in average follow-up costs (EVAR €1,656; OSR €499). Follow-up costs includes only the costs of diagnostic procedures (CT or duplex) and outpatient visits of surviving patients; the costs of complications and reinterventions were excluded in these calculations but included in the total costs.

In summary, EVAR and OSR can be considered equally effective (0.035), while EVAR is cost-saving (€-1,112) compared with OSR.

Sensitivity and scenario analyses

Table 7.4 and Figures 7.3 and 7.4 present the results of the uncertainty analyses. The tornado diagram (Figure 7.3) presents the impact of the uncertainty per parameter (one-way sensitivity analyses) or scenario on either the incremental costs, incremental QALYs and the ICER.

Univariate sensitivity analyses

The price of an EVAR device and the number of ICU days after EVAR and OSR showed the greatest influence on the incremental costs (Figure 7.3). Increases in the number of ICU days after EVAR meant that EVAR was no longer cost-saving compared with OSR (incremental costs €5,361). The most influential parameter on the ICER was the hazard ratio of cardiovascular events.

Scenario analyses

In the base-case analysis, we assumed that there was no difference in QoL between the treatment groups after 18 months. When we increased this period to 24 months and 36 months, we found a reduction in QALY gain (0.02 and 0.017, respectively). When the QoL results from the EVAR-1 trial was used, this led to a QALY increase (0.060) since that study found that QoL was equal after 36 months and the QoL gain of EVAR versus OSR at 1 month follow-up was larger than that was used in the base-case analysis. An alternative approach to model survival based on the EVAR-1 trial resulted in an increase in QALY gain (0.116) since the survival benefit continued during the remaining life-years; consequently, EVAR became even more cost-effective compared with OSR.

A scenario analysis showed that EVAR was more effective (0.068 QALYs) in 80 year old patients since the initial gain in survival increases by age, as presented by Schermerhorn et al.[142]. Furthermore, the duration of survival benefit increases by age; 80-year-old EVAR and OSR patients showed an equal survival rate of 68% after 4 years, much longer than the duration seen with younger patients. For 65 year old patients, EVAR led to a QALY increase of 0.0375 and incremental costs of €-723.

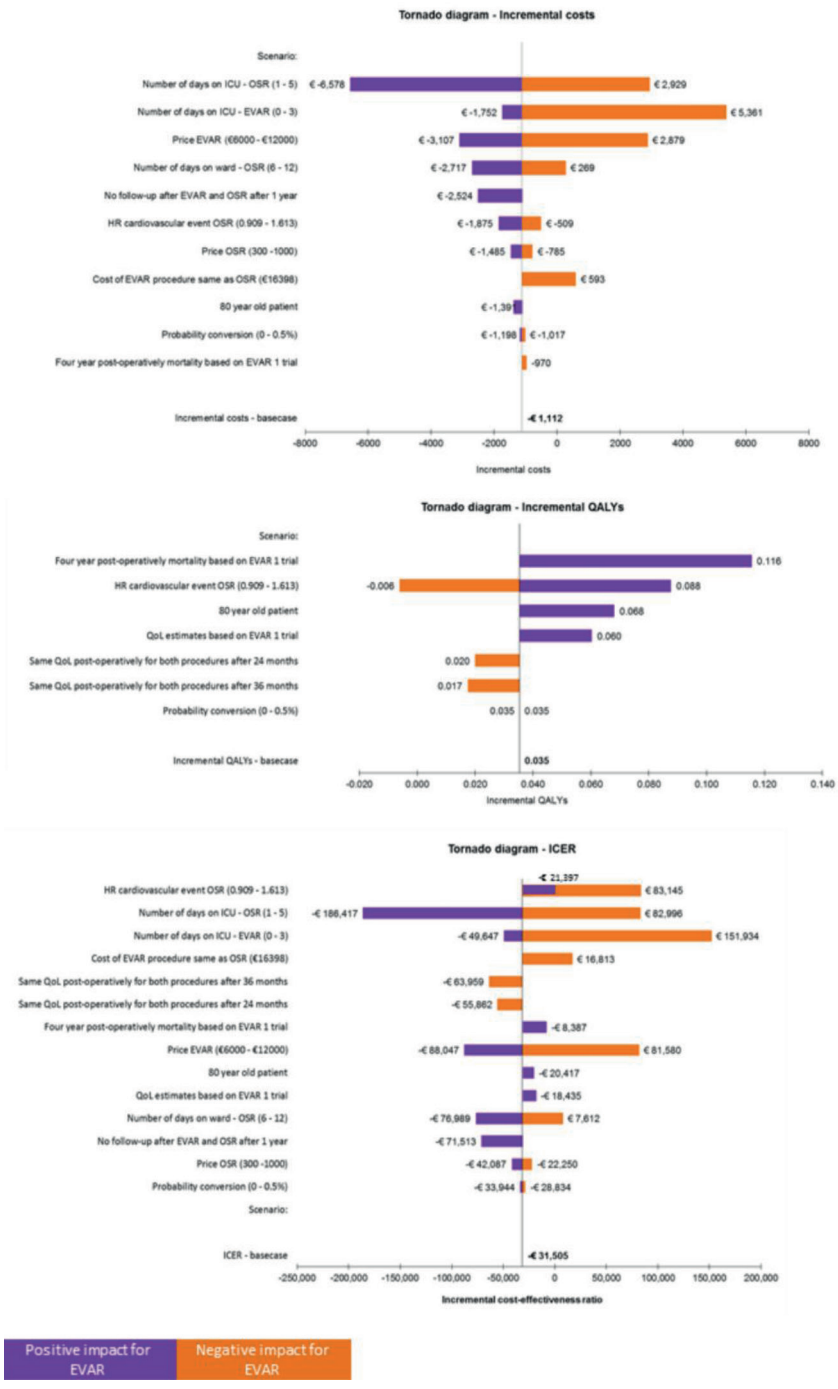

Figure 7.3 | Tornado diagrams

EVAR: endovascular aneurysm repair; HR: hazard rate; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; OSR: open surgical repair; QoL: quality of life

Table 7.4 | Base-case analysis and scenario analyses

Base-case*				Scenario 1: 80y old patient			Scenario 2: 65y old patient			Scenario 3: EVAR 1 QoL			Scenario 4: EVAR 1 mortality			Scenario 5: DREAM trial QoL 36 months		
QALYs	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**
30 days	0.040	0.034	**0.006**	0.037	0.031	0.006	0.040	0.034	0.0058	0.044	0.037	0.007	0.040	0.034	0.006	0.040	0.034	0.006
1 year	0.514	0.497	**0.017**	0.472	0.441	0.031	0.514	0.498	0.0163	0.498	0.461	0.037	0.512	0.492	0.020	0.514	0.497	0.017
2 years	1.039	1.026	**0.013**	0.944	0.900	0.043	1.039	1.027	0.0126	0.996	0.957	0.039	1.036	1.011	0.025	1.030	1.034	-0.005
5 years	2.300	2.276	**0.024**	2.021	1.958	0.063	2.354	2.330	0.0238	2.186	2.136	0.050	2.299	2.239	0.060	2.291	2.285	0.006
30 years	4.704	4.669	**0.035**	3.043	2.975	0.068	6.065	6.027	0.0375	4.452	4.392	0.060	4.715	4.599	0.116	4.695	4.677	0.017
Life-years	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**
30 days	0.083	0.081	**0.002**	0.082	0.078	0.004	0.083	0.081	0.002	0.083	0.081	0.002	0.082	0.080	0.002	0.083	0.081	0.002
1 year	0.960	0.941	**0.019**	0.943	0.897	0.046	0.961	0.942	0.018	0.960	0.941	0.019	0.958	0.933	0.025	0.960	0.941	0.019
2 years	1.854	1.828	**0.026**	1.802	1.722	0.080	1.855	1.829	0.026	1.854	1.828	0.026	1.849	1.803	0.046	1.854	1.828	0.026
5 years	4.102	4.076	**0.026**	3.770	3.672	0.098	4.102	4.077	0.026	4.102	4.076	0.026	4.102	4.013	0.089	4.102	4.076	0.026
30 years	8.674	8.648	**0.026**	5.701	5.603	0.098	11.025	11.000	0.026	8.674	8.648	0.026	8.696	8.522	0.174	8.674	8.648	0.026
Costs	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**	**EVAR**	**OSR**	**Δ**
30 days	€16,109	€18,023	**€-1,914**	€16,097	€17,961	€-1,863	€16,114	€18,037	€-1,922	€16,109	€18,023	€-1,914	€16,097	€18,006	€-1,909	€16,109	€18,023	€-1,914
1 year	€16,726	€18,614	**€-1,888**	€16,701	€18,520	€-1,819	€16,732	€18,628	€-1,896	€16,726	€18,614	€-1,888	€16,712	€18,590	€-1,878	€16,726	€18,614	€-1,888
2 years	€17,488	€19,287	**€-1,179**	€17,433	€19,153	€-1,720	€17,493	€19,300	€-1,807	€17,488	€19,287	€-1,179	€17,473	€19,253	€-1,780	€17,488	€19,287	€-1,799
5 years	€19,569	€21,278	**€-1,709**	€19,273	€20,905	€-1,632	€19,573	€21,289	€-1,715	€19,569	€21,278	€-1,709	€19,561	€21,213	€-1,652	€19,569	€21,278	€-1,709
30 years	€24,483	€25,595	**€-1,112**	€21,383	€22,774	€-1,391	€27,018	€27,741	€-723	€24,483	€25,595	€-1,112	€24,500	€25,469	€- 969	€24,483	€25,595	€-1,112

Table 7.4 | *(Continued)*

Base-case*		Scenario 1: 80y old patient	Scenario 2: 65y old patient	Scenario 3: EVAR 1 QoI	Scenario 4: EVAR 1 mortality	Scenario 5: DREAM trial QoL 36 months
ICER (QALY)						
30 days	**Dominant (€-322,730)**	Dominant (€-287,690)	Dominant (€-330,633)	Dominant (€-290,867)	Dominant (€-320,765)	Dominant (€-322,730)
1 year	**Dominant (€-112,474)**	Dominant (€-58,449)	Dominant (€-116,355)	Dominant (€-50,901)	Dominant (€-92,331)	Dominant (€-112,474)
2 years	**Dominant (€-137,077)**	Dominant (€-39,815)	Dominant (€-143,929)	Dominant (€-45,653)	Dominant (€-71,462)	€376,032
5 years	**Dominant (€-71,233)**	Dominant (€-26,049)	Dominant (€-72,221)	Dominant (€-34,422)	Dominant (€-27,592)	Dominant (€-280,726)
30 years	**Dominant (€-31,505)**	Dominant (€-20,417)	Dominant (€-19,272)	Dominant (€-18,435)	Dominant (€-8,387)	Dominant (€-63,959)

* 72y, 87% men, QoL DREAM trial 18 months, Schermerhorn et al. [142] short term mortality

EVAR: endovascular aneurysm repair; ICER: incremental cost-effectiveness ratio; OSR: open surgical repair; QALY: quality adjusted life years; QoL: quality of life

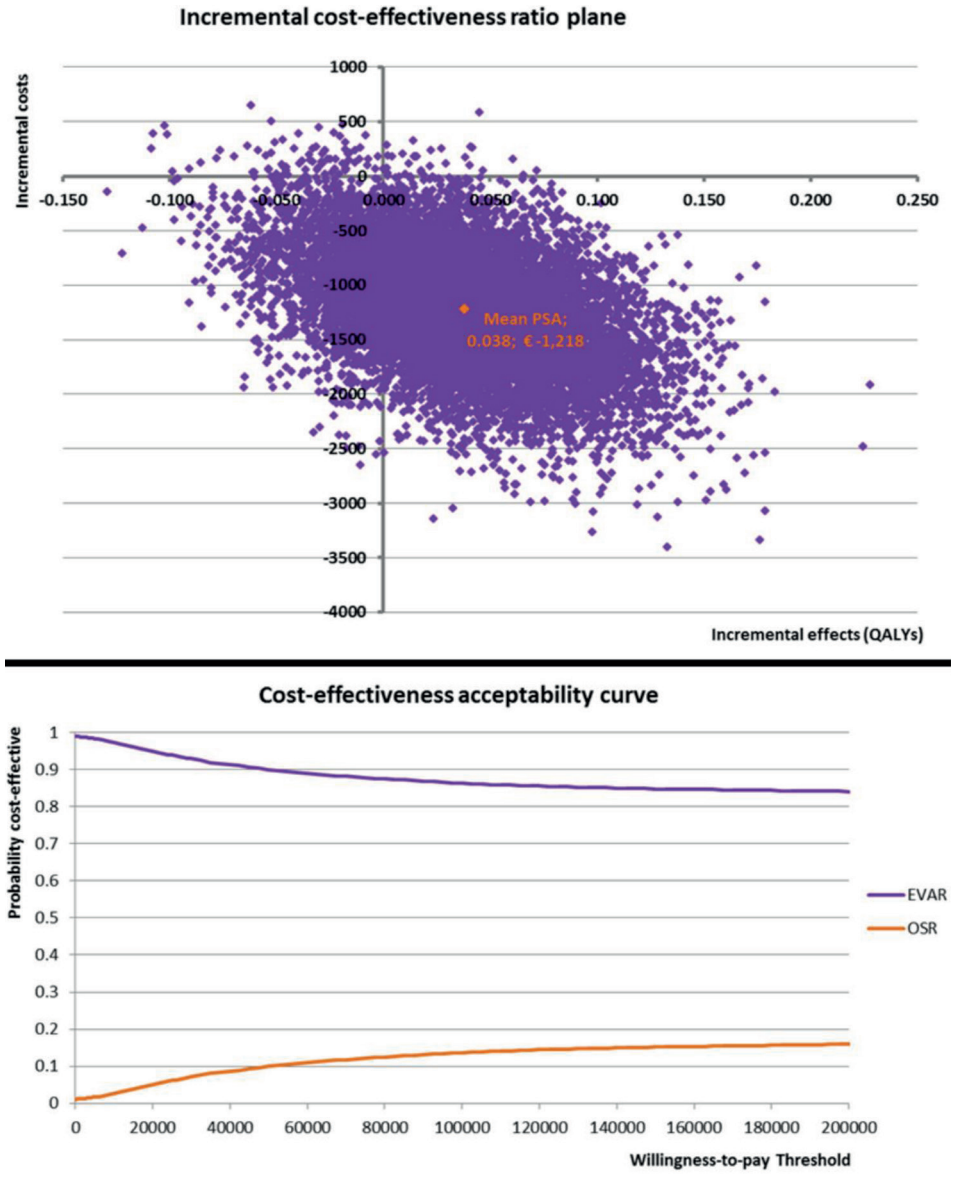

Figure 7.4 | ICER plane and CEAC

EVAR: endovascular aneurysm repair; OSR: open surgical repair; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life years

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis (Figure 7.4) showed that in 81% of the simulations EVAR was more effective and cost-saving compared with OSR, while in 17.9% of the simulations EVAR was less effective but cost-saving. In only 1.1% of the simulations the ICER was located in the north-west (0.3%) or north-east (0.8%) quadrant, meaning that EVAR was very unlikely to be more expensive than OSR. As can be seen from the ICER plane, the incremental costs and effects are negatively correlated. If the chance of experiencing an event after EVAR decreases, the total costs of EVAR will decrease and the total QALYs after EVAR will increase. The CEAC (Figure 4) presents the chance that EVAR is cost-effective at a particular willingness-to-pay threshold and shows that EVAR remains the most cost-effective strategy regardless of the threshold. If a willingness to pay threshold of €20,000 or €80,000 per QALY gained[168] are used, EVAR has a high probability (95% and 87.5%, respectively) of being cost-effective compared with OSR.

DISCUSSION

This cost-utility analysis estimated the lifetime cost-effectiveness of elective EVAR compared with elective OSR in patients with AAA for a Dutch setting. In the base-case analysis, EVAR was more effective than OSR (difference of 0.035 QALYs) over a lifetime time horizon, due to the initial survival gain in the first 2 years and the reduction in events. EVAR and OSR can be considered equally effective since the gain in QALYs is minimal and the uncertainty analyses (PSA) showed a large variation in effectiveness (range: -0.129, 0.228 QALY). However, EVAR can be cost-saving (€-1,218) compared with OSR (range: €-3,397, €655) due to a shorter hospitalization. Scenario analyses showed that EVAR becomes more effective versus OSR when used in older patients, when QoL is based on the EVAR-1 trial[137] or when mortality is based on the EVAR-1 trial[143].

In line with our results, many of the previous economic evaluations comparing elective EVAR with elective OSR concluded that EVAR was more effective than OSR[95,140,161,162,169-171], with health gain ranging from 0.0012 to 0.42 QALYs. However, four studies estimated a QALY loss for EVAR[143,144,156,161] (range: -0.01,-0.042). The QALY loss estimated by Brown et al.[143], Epstein et al.[161] and Epstein et al.[156] was the result of assuming that the all-cause survival at 2 years or 8 years follow-up were equal for EVAR and OSR, and assuming a greater hazard of late AAA deaths after EVAR. Prinssen et al.[144] also found that the initial survival gain was offset by a later increase in mortality, which resulted in a negligible survival advantage. In our study, we used age-specific data from Schermerhorn et al.[142], who found that mortality converged at 23 months, 48 months and 51 months for patients with a baseline age of 67–74 years, 75–84 years and 85+ years, respectively. Thereafter, survival was equal between the EVAR and OSR patient groups. Use of this data improves the effectiveness of EVAR compared with the methods used by the

previously mentioned studies[143,156,161]. However, other studies[172] have also assumed an equal survival after a specific time period or assumed that the initial benefit of EVAR continued without any convergence (catch-up) in survival.

Most previous economic evaluations have reported that the total costs of EVAR were higher than those of OSR[95,140,144,161,162,169,170,172,173], mainly due to the higher device costs. However, in four studies[161,171,173,174] EVAR was considered cost-saving since the initial admission costs of EVAR were lower than those of OSR due to a reduction in hospital days. In our study, the higher costs of the device were offset by the reduction in hospitalization days and an EVAR procedure was less expensive than OSR. Consequently, EVAR was cost-saving over a lifetime time horizon compared with OSR.

Most studies[140,143,144,156,161,170,172,173] concluded that EVAR is not cost-effective compared with OSR due to the high costs of an EVAR procedure; some studies also found that EVAR was associated with a slight QALY loss. In contrast, we concluded that EVAR and OSR were equally effective and EVAR was cost-saving compared with OSR which was the result of the lower procedure costs. The number of hospital days after EVAR used in our study is somewhat lower than in other cost-effectiveness studies since those studies used resource use data from older clinical studies. The length of hospitalization has declined remarkably since the first generation of EVAR devices. Physicians are more experienced with an EVAR and the newer generations lead to fewer peri-operative and post-operative complications.

Strengths & limitations

This study used long-term results from a large registry from the US[142,148], which were considered applicable to the Dutch setting for a number of reasons: 1) the results were based on a very large population (n=45,660) with six-year follow-up, 2) the large number of clinical events, and 3) mortality results were presented for different age categories. This registry provides good insights into the events that can occur during the first 30 days after the procedures as well as the reinterventions that may take place up to six years follow-up. Consequently, our study was able to incorporate many clinical events that were significantly different between procedures and thereby estimate a more realistic incremental cost-effectiveness ratio. However, the earlier cohort of the US registry[142,148] also included patients who underwent EVAR using early generation devices which may have led to an overestimate of the reintervention rate in the EVAR group and an underestimate of the QALY gain of EVAR compared to OSR.

The procedure costs estimated alongside the clinical trials were not considered applicable for the following reasons: 1) resource use and unit costs were considered outdated (e.g. length of stay) or 2) resource use and unit costs were based on another country. Therefore, the resource use was based on a Dutch registry, reporting outcomes from 2013[165] from daily practice and not from

a randomized study. Resource use of the registry was combined with the Dutch costing manual[153] to estimate the costs that reflect current treatment practice.

It is important to recognize that the use of data from the older studies like EVAR-1[137] could lead to different results (and therefore conclusions). However, the results of older studies may say very little about the current cost-effectiveness of EVAR versus OSR since newer devices have a better technical performance and physicians are more experienced with EVAR. One factor that affects the cost difference is the length of hospital stay following EVAR, which has decreased considerably over the years. Cost-effectiveness analyses based on older studies may present results that may not reflect the 'real' cost-effectiveness of EVAR nowadays.

Brown et al.[143] included the chance of death while waiting for the procedure since they believed that excluding it could lead to bias. However, we did not include the chance of events before the procedure since the clinical experts were of the opinion that there was no difference between the procedures in mortality, waiting time and QoL. Consequently, the incremental survival between OSR and EVAR are correct but it may be possible that survival per strategy is somewhat lower.

The short-term (30 days) clinical events were based on Schermerhorn et al.[142]. One could argue that this study reported (non-)fatal events, which may lead to an overestimation of the clinical events for both treatment groups. However, the impact of this assumption will be minimal since short term clinical events are only included for patients who have survived the first 30 days.

OSR has been associated with sexual dysfunction[175] which may reduce QoL. Although sexual functioning was not explicitly incorporated in our analysis, it may have been included in the analysis because of our use of prospectively collected QoL (EQ-5D) data from the DREAM trial[136], although the EQ-5D may not be sufficiently sensitive to changes in sexual functioning. Any steps to include sexual functioning more adequately would likely result in more favourable results for EVAR.

This study assessed the cost-effectiveness of EVAR versus OSR in patients fit and anatomically suitable for both procedures. Some of the input values used in our analyses were based on the EVAR-1 trial[143], which involved the selection of a small subgroup of the AAA population since patients needed to be fit for both procedures. Consequently, the effectiveness of EVAR and OSR can vary across the AAA patient population. EVAR will be more effective if it was compared to surveillance in patients who were not fit for OSR due to comorbidities.

Furthermore, input data was based on published literature and the proportion men included in these studies is approximately 85%–95% since AAA is more common in men than in women. This study has estimated in the base case the cost-effectiveness of EVAR for a cohort of patients

with an average age of 72 years and 87% was men based on the DSAA registration[165]. The cost-effectiveness of women with AAA electively treated with EVAR or OSR should have been investigated separately but no information specific for women is available.

The Dutch guidelines for pharmacoeconomic research recommend the use of a societal perspective when assessing the cost-effectiveness of an intervention[146]. In this study we did not include productivity costs, travel costs and informal caregiver burden since we assumed that this is comparable between the two strategies. Prinssen et al.[144] have included productivity costs and concluded that the OSR group (€363) had higher productivity costs than the EVAR group (€243). Tarride et al.[173] estimated a difference of $16 between the patients groups. However, the proportion of patients with paid employment is relatively low since these patients are generally older than 65 years. Therefore, the difference in productivity costs will be minimal as estimated by Tarride et al.[173] and Prinssen et al.[144]. Travel costs, indirect medical costs, and informal caregiver burden were not included in these two studies but it is reasonable to assume that indirect costs and outcomes will not influence the cost-effectiveness of EVAR. However, further research is required to estimate the impact of EVAR versus OSR on informal caregiver burden and indirect medical costs.

This study used several sources and assumptions to estimate the cost-effectiveness of EVAR versus OSR. The combination of data from multiple sources could be viewed as a limitation because it could lead to a biased estimate of EVAR's cost-effectiveness. We therefore conducted various sensitivity analyses to assess the robustness of our results and to quantify the degree of uncertainty. However, we do believe that EVAR and OSR can be considered equally effective. Furthermore, due to reductions in hospital days and complications EVAR was cost-saving.

Implications

In 2013, 72%[145] of the Dutch patients with AAA treated electively are undergoing EVAR. Various factors influence the procedure that a patient receives; the costs of a procedure and the 30-day mortality are just two of them. Clinicians are more likely to choose EVAR for patients suitable for both procedures because it is less invasive. Based on expert opinion, patients only undergo OSR when they are anatomically unsuitable for EVAR, very young or if a patient prefers OSR over EVAR.

Patient are more likely to prefer EVAR over OSR since people are often risk-averse meaning that they would avoid the short term higher 30-day mortality of OSR even when they know that mortality converges after some years.

Conclusions

This study showed that EVAR and OSR can be considered equally effective and that EVAR can be cost-saving compared with OSR. Therefore, EVAR can be considered as a cost-effective solution for patients with AAA. However, the cost-effectiveness of EVAR is highly dependent on the price of the EVAR device and the reduction in hospital days, complications and 30-day mortality.


Challenges
Modelling
Tests
Devices
Cardiovascular
Technologies
ICER
QALY
Analyses
Markov
Cost-effectiveness
Data
Blood
Disease
Costs
Results
Extrapolating
CVD
Thesis
PCI
CAD
Drugs
Diagnosis
Intervention
Follow-up
Specificity
Sensitivity Analyses
Scenario Analyses
Guidelines
TAVI
Angina
EVAR
RCT
Prevention
Validity
Bias
Stroke
Literature
Precision
Identification
Structure
Efficacy
Persistence
Frequency
Budget
Survival
Observational
Review
Risks
Decision Tree
Prior Likelihood
Gold Standard
False Negative
True Negative
False Positive
True Positive
Real-world
Care Pathway
Prevalence
Probabilities
Learning Curve
Monitoring
Statistics
Indication
Limitations
Transition
Recommendations
Importance
Accuracy
CT-scanner
Synergy
Artery
Outcomes
QoL
Fevar
Cerebrovascular
Diastolic
Ischemic
Short Term
Balloon
Surgical
Simplification
Heart
Bevar
DES
ICA
CABG
Systolic

Chapter 8

Modelling the cost-effectiveness of fenestrated and branched endovascular aneurysm repair for juxta-renal and thoraco-abdominal aneurysms

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Armstrong N, Burgers LT, Deshpande SN, Al MJ, Riemsma R, Vallabhaneni SR, et al.The use of fenestrated and branched endovascular aneurysm repair for juxtarenal and thoracoabdominal aneurysms: a systematic review and cost-effectiveness analysis. Health Technol Assess 2014;18(70)

ABSTRACT

Background: Patients with juxta-renal (JRAAA) or thoraco-adbominal aortic (TAAA) aneurysms requiring treatment may undergo open surgical repair (OSR) or a complex endovascular aneurysm repair (EVAR) such as a fenestrated (fEVAR) or branched EVAR (bEVAR). This article describes and discusses potential methods of evaluating the cost-effectiveness of fEVAR/bEVAR in JRAAA and TAAA and the challenges in that assessment.

Methods: This study has four steps: literature review of (cost-)effectiveness, design of mathematical model, populating the model, and analysis.

Results: The framing phase showed that fEVAR/bEVAR in JRAAA/TAAA should be evaluated for two populations: 1) fEVAR/bEVAR versus OSR in patients fit for OSR, and 2) fEVAR/bEVAR versus no surgery in patients unfit for OSR. The literature reviews in the assessment phase yielded no relevant studies. We constructed two related models: a short-term (30-day) model of costs and effectiveness and a long-term model estimating lifetime costs and effectiveness beyond 30 days. Both models include complications, reinterventions and mortality. In the end, we concluded that a cost-effectiveness analysis would not be meaningful because of insufficient effectiveness evidence, large variation in technical features regarding fEVAR/bEVAR stent-grafts, and rapid changes in fEVAR/bEVAR technology.

Conclusion: It is currently impossible to estimate the cost-effectiveness of fEVAR or bEVAR. Their cost-effectiveness and the related uncertainty can only be evaluated if there is some evidence on the effectiveness and costs of fEVAR/bEVAR. The model developed in this study can be used to determine which data should be collected to ensure a proper assessment of fEVAR/bEVAR.

INTRODUCTION

Standard endovascular aneurysm repair (EVAR) is an established choice of treatment for abdominal aortic aneurysm (AAA) in anatomically suitable patients, with certain advantages over open surgical repair (OSR). However, standard EVAR is not feasible in complex aneurysms such as juxta-renal (JRAAA), para-renal and thoraco-abdominal aortic aneurysms (TAAA). Advanced endovascular technologies such as fenestrated and branched EVAR (fEVAR/bEVAR) have been developed over the last decade for such patients. Although fEVAR/bEVAR was originally used predominantly in patients considered physiologically unfit for OSR, fEVAR/bEVAR are now a frequently chosen option for most patients.

Many observational studies[176-178] and case series have observed a reduction in mortality and morbidity after fEVAR/bEVAR compared with OSR, despite fEVAR/bEVAR patients being older and having more co-morbidities. However, a thorough investigation of its comparative effectiveness [e.g. a randomized controlled trial (RCT)] versus open repair has never been conducted. In addition, it is not appropriate to extrapolate the results of randomized controlled trials of EVAR for infrarenal aneurysms since performing an OSR in patients with JRAAA or TAAA is associated with a higher perioperative mortality risk and increased use of critical care compared with OSR in infrarenal AAA patients.

The use of fEVAR/bEVAR techniques has increased rapidly over the last decade and continues to increase, despite uncertainties in their comparative effectiveness[13]. Therefore there is a need to examine the value of fEVAR/bEVAR in a comprehensive manner. With this in mind, the National Institute for Health Research (NIHR) Health Technology Assessment programme began a 'short report' in 2013 on the cost-effectiveness of fEVAR/bEVAR in JRAAA and TAAA. This article describes and discusses our attempt to assess the cost-effectiveness of fEVAR/bEVAR in that study[13] and the challenges that arose during the assessment.

METHODS

The estimation of the cost-effectiveness of fEVAR and bEVAR from an UK NHS perspective was performed in two phases: framing phase and assessment phase. These phases can be compared with the first two phases that are used in a NICE technology appraisal process; scoping and assessment. Since this study was a short report performed for NIHR, it was based on the same methodology.

In the first "framing" phase, the boundaries of the study were set and justified[179]. Key points that are considered in the framework are: 1) objective of the analysis, 2) audience for the evaluation,

3) viewpoint of the analysis, 4) analytic time horizon, 5) target population, 6) intervention, and 7) alternative interventions for comparison[179]. These key points can be compared with the issues that need to be addressed in the scoping phase of a NICE appraisal[180].

The second "assessment" phase, was divided into four separate steps: 1) systematic review of current evidence on the effectiveness and cost-effectiveness, 2) development of the structure of the model, 3) populate the model, and 4) analyses. Although a systematic review is a mandatory component of a full technology assessment report, it is not required in an economic evaluation[180]. We nevertheless conducted a systematic review to avoid any possibility of 'cherry picking' of values for input parameters, in line with the ISPOR Taskforce Reports on 'modeling good research practices'[132].

Both the clinical and cost-effectiveness reviews are conducted according to NICE guidelines[180]. The effectiveness review focused primarily on studies reporting on RCT data comparing fEVAR/bEVAR with OSR or no surgery since these studies provided the most valid evidence of relative efficacy. If no RCTs were identified, the review was to be extended to include (non-randomized) comparative studies. Potential bias arising from the study design of these studies was explored. The synthesis of outcome data was performed using a meta-analysis when sufficient relevant and valid data is available. The cost-effectiveness review focuses on studies evaluating the cost-effectiveness of fEVAR/bEVAR. Furthermore, studies reporting on useful outcomes [e.g. quality of life (QoL), costs, resource use or transition probabilities (e.g. reinterventions)] to inform the decision model are also potentially relevant.

The cost-effectiveness analysis (CEA), the last three steps of the assessment phase, was conducted according to the NICE guide to the methods of technology appraisal[180]. Specific requirements (e.g. discount rate, time horizon and perspective) are recommended in this guideline.

RESULTS

1 | Framing phase

Objective and audience

The objective of this study is to inform the NHS on the cost-effectiveness of fEVAR/bEVAR in patients diagnosed with JRAAA or TAAA.

Disease and population

Patients with an enlarged AAA (diameter >5 cm) located close to the origin of the renal arteries, juxta-renal or in both the thoracic and abdomen are diagnosed with JRAAA or TAAA, respectively. Those patients can be divided in two main groups, those fit for OSR and those unfit for OSR.

Without the existence of the interventions fEVAR or bEVAR, patients would be treated with an OSR if considered to be fit enough. Patients who are not fit for OSR would be treated with no surgery, i.e. best medical therapy. Fitness of patients for an OSR can be determined based on the fitness criteria that were used for the EVAR trials[143], which evaluated EVAR with either OSR (EVAR-1 trial[181]) or medication (EVAR-2 trial[182]) for the treatment of AAA depending on the fitness of the patient. Patients were considered unfit for OSR if a patient had 1) an American Society of Anaesthesiology (ASA) grade of IV, 2) cardiac symptoms, 3) renal symptoms, or 4) respiratory symptoms. However, these guidelines to determine the fitness for OSR were subject to treatment variation[143]. Aneurysm size was also important for determining the fitness of a patient since patients who were earlier described as 'unfit for open repair' and later developed a larger aneurysm were suddenly deemed 'fit for the procedure'[143].

Potentially, subgroups can be determined by age, gender, whether dialysis dependent, aneurysm size, fitness, number of target vessels, whether elective or emergency and symptomatic versus non-symptomatic since these characteristics may have a substantial impact on the cost-effectiveness. Furthermore, the type of OSR can also lead to differences in perioperative mortality[176] and consequently in the cost-effectiveness of fEVAR/bEVAR.

Interventions and comparators

Based on the fitness for OSR two treatment comparisons for this population were evaluated: 1) fEVAR/bEVAR versus OSR and 2) fEVAR/bEVAR versus no surgery.

fEVAR and bEVAR are specially manufactured stent-grafts with openings to allow blood to reach branches of the aorta[13]. This procedure is performed endovascular and is therefore less invasive than OSR since during an OSR an aortic clamp must be placed leading to cardiovascular instability and stress. Also, open surgery for TAAA frequently requires cardiopulmonary bypass and on occasion circulatory arrest. The no surgery strategy can be defined as optimal conservative care, i.e. patients should receive statins, beta-blockers, antihypertensives, antiplatelets, and/or lifestyle advice. Full descriptions of the interventions are reported in the full report[13]. Ideally, the cost-effectiveness of fEVAR and bEVAR should be evaluated separately since the morbidity and mortality may differ between procedures, however this was not possible.

Complications due to a fEVAR/bEVAR procedure that can occur peri-operatively or post-operatively are 1) aneurysm or laparotomy related reinterventions (e.g. conversion from endovascular repair to open repair, bowel resection, amputation of the lower leg) and 2) medical complications (e.g. myocardial infarction (MI), stroke, deep venous thrombosis (DVT), pulmonary embolism, pneumonia, renal failure). Patients undergoing OSR are associated with higher short-term mortality and medical complications; however aneurysm-related reinterventions are more frequently performed in patients undergoing endovascular repair[142].

Viewpoint, health outcome measures and costs

The CEA, steps three and four of the assessment phase, estimates the costs from a NHS and personal and social services perspective; i.e. including all direct costs. It is required to draw data for the costs from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), and expert opinion where necessary. Adopting the NHS perspective implies that all direct health effects (quality adjusted life years), whether for patients or other people, of all treatment strategies need to be estimated. According to the NICE guidelines, costs and outcomes need to be discounted at 3.5% per year[180].

Analytic horizon

The costs and outcomes in the CEA are preferably estimated for a time horizon that is long enough to reflect all important differences in costs and outcomes between the technologies being compared. FEVAR/bEVAR, OSR and no surgery do lead to differences in survival or benefits that persist for the remainder of a person's life and thus a lifetime time horizon is required.

2 | Assessment phase

2.1 | Systematic review of currently available evidence

As part of the assessment phase, two systematic reviews were performed on the clinical effectiveness and cost-effectiveness of fEVAR/bEVAR. The systematic review on clinical effectiveness showed that there were no prospective comparative studies of fEVAR/bEVAR in either those fit or unfit for OSR[13]. Treatment allocation was based on physician or patient preferences and not randomized (based on chance) and therefore patient groups were not comparable (i.e. age and comorbidities) leading to bias. Thus, no source of information on efficacy of fEVAR/bEVAR in preventing mortality and serious complications in direct comparison to OSR was available. The cost-effectiveness review resulted also in zero included studies focussing on the costs, effectiveness or cost-effectiveness of fEVAR/bEVAR, OSR or no surgery in JRAAA or TAAA patients. The full report contains the full searches and results of both reviews[13].

2.2 | Structure of the model

A decision model was created since no existing studies evaluating the cost-effectiveness of fEVAR/bEVAR were found. The model consists of two separate models for both short-term and long-term outcomes. The short-term model, a decision tree, estimates costs and effects pre-operatively (including the effect of waiting time), intraoperative, and post-operative up to 30 days. A long-term model estimates the lifetime costs and effects of the individuals who have survived the initial procedure and the 30 day post-operative period. The long-term model structure is adopted from previously published HTA reports for the evaluation of EVAR by Brown et al.[143] and Chambers et al.[183] since it is likely that the treatment and disease pathways of EVAR and fEVAR/bEVAR are comparable, even if the input parameters are not. See Appendix 2 of the full report[13] for the quality of these studies based on the Drummond et al. checklist[184].

Model structure | short-term model (fit for OSR)

Figure 8.1 shows the structure for a short-term decision model for this comparison. It is likely that patients have to wait until the actual surgery (OSR or fEVAR/bEVAR) can be performed. In particular, patients who will be treated with fEVAR or bEVAR have to wait since a large proportion of the patients will have to wait for custom-made devices while the inventory of off-the-shelf devices is expanding. The inclusion of *waiting time* in the model was deemed to be important since a difference in waiting time could lead to differences in mortality.

Patients who actually receive fEVAR or bEVAR may later switch to an OSR due to problems such as an endoleak or stent-graft migration, therefore it was important to incorporate these *conversions* into the model. Based on a study evaluating the cost-effectiveness of EVAR[183], it was assumed that the conversion took place during the time-span of the short term model and that it was not possible that patients undergoing OSR are converted to EVAR.

Furthermore, mortality (all-cause and aneurysm related) and complications during the first 30 days are incorporated in the short-term model. Medical complications can be categorised into four types: cardiac complications (e.g. myocardial infarction, DVT), pulmonary complications (e.g. pneumonia), renal complications (e.g. renal failure), and neurological complications (e.g. stroke). Furthermore, aneurysm-related and laparotomy related reinterventions are also incorporated in the model structure. A reintervention for patients who underwent fEVAR or bEVAR could either be an OSR or again an endovascular procedure. Reinterventions are included as complications.

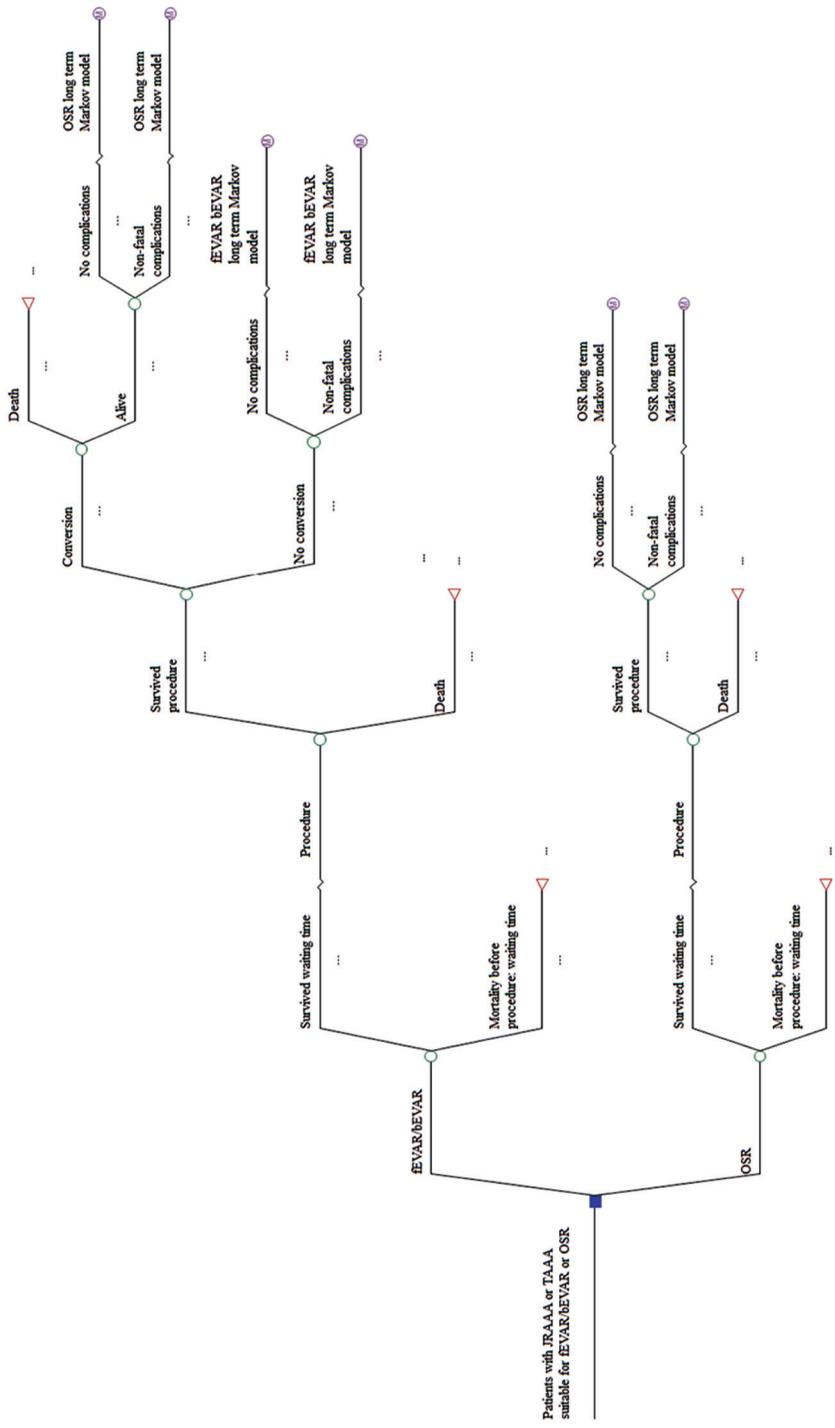

Figure 8.1 | Short-term model (fit for OSR)

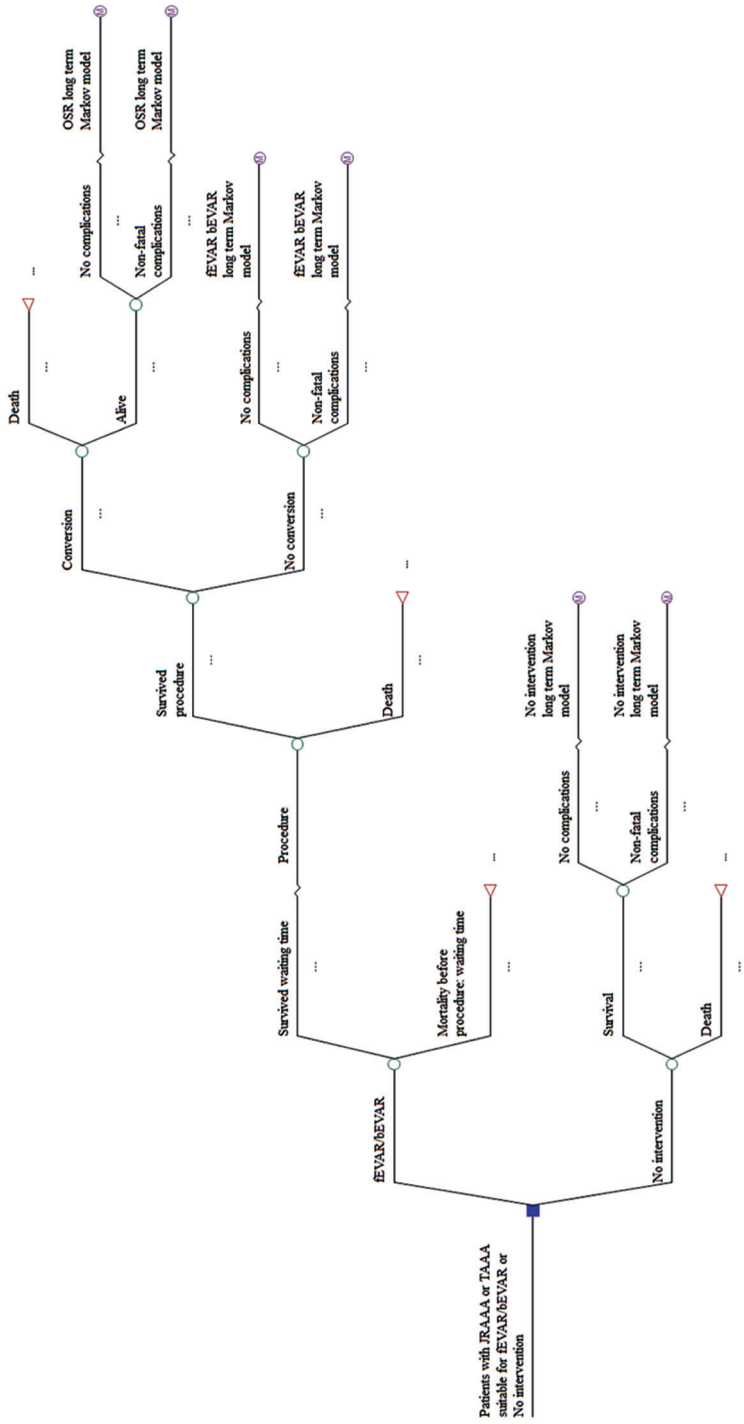

Figure 8.2 | Short-term model (unfit for OSR)

Model structure | short-term model (unfit for OSR)

The same assumptions described above for those fit for OSR apply for patients unfit for OSR. Waiting time is not an issue for patients treated with medication only and in some cases conversion from fEVAR or bEVAR to OSR might not be possible since patients are considered not fit for OSR. Figure 8.2 shows a structure for a short-term decision model for this comparison.

Model structure | long term model

The long-term model estimates lifetime costs and effects of patients who have survived the waiting time before the procedure and the 30-day post-operative period. For such a long-term model, a Markov model seems most appropriate (Figure 8.3). This model consists of two chronic health states: 1) event-free and 2) (non-)aneurysm related death and this structure is similar to the economic evaluation of EVAR versus OSR presented by Chambers et al.[183]. Patients start out in the event-free state and have a risk of a non-fatal event leading to readmission. Patients may be readmitted to the hospital if, for example, a reintervention is required. Note that the readmission state is a temporary health state: after the readmission patients move back to the event-free state. Eventually, all patients will die from aneurysm-related causes or other causes.

As in the economic evaluation by Chambers et al.[183] it was assumed that patients who convert from EVAR to OSR during the primary admission have the same long-term prognosis as patients initially undergoing OSR.

The cycle length needs to be short enough to ensure that no more than one event occurs during one cycle. A cycle length of 6 months was considered appropriate according to the timing of the events used by Brown et al.[143]. A half-cycle correction was incorporated and thus it was assumed that transitions occur half-way through the cycle.

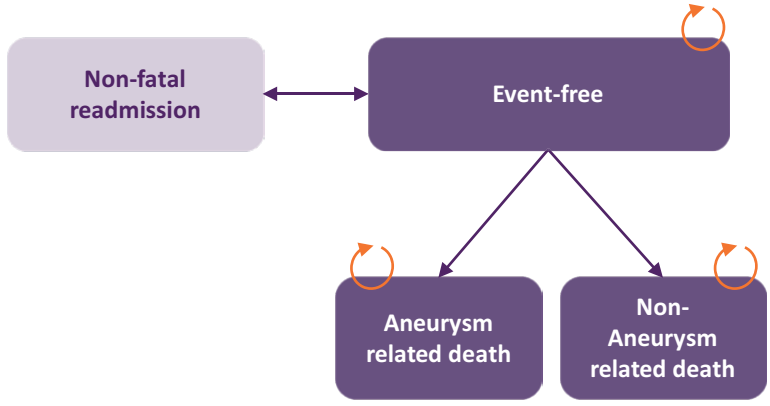

Figure 8.3 | Long term model

2.3 | Input parameters

The third step in the assessment phase is to populate the previously proposed model. Estimates for the input parameters need to be provided by the systematic reviews on clinical effectiveness and cost-effectiveness, literature or expert opinion. Two experts were consulted; however these experts were of the opinion that it was not feasible to provide valid estimates for the input parameters since there exists vast variation in stent-grafts used between patients and between centres. Since no studies were included in the systematic reviews and we were unable to receive estimates from clinical experts we were not able to complete this third step. Nevertheless, suggestions on parameters that need to be included are provided below.

Transition probabilities

For the short-term model (Figures 8.1 and 8.2) it is important to collect data in the period before the treatment during waiting time and up to 30 days after the procedure. Data concerning mortality, conversions, reinterventions, and complications are important for this model. The structure of the long-term model (Figure 8.3) requires three time-dependent transition probabilities: 1) non-aneurysm related mortality, 2) aneurysm related mortality, and 3) non-fatal readmissions. These transition probabilities need to be based on general population mortality estimates[185] (non-aneurysm related mortality) and on clinical effectiveness data from comparative studies.

Patients could be readmitted due to a clinical event but also to undergo a reintervention. Brown et al.[143] did not incorporate clinical events such as MI or stroke in the model since there was no significant difference between the treatment strategies (OSR versus EVAR) in the EVAR-1 trial. While this assumption might be valid for the evaluation of EVAR, the results of clinical studies will show if this assumption also holds for an evaluation of fEVAR or bEVAR. Moreover, an RCT is likely to be underpowered to detect significant effects for these events. Generally, when events like MI or stroke are considered clinically relevant, they should be included in the long-term model since such clinical events have a substantial impact on the quality of life of patients and healthcare costs. Furthermore, the impact of radiation of the CT scans used during follow-up and of the fluoroscopy used during the interventions could be incorporated in the model if this is deemed important. However, the mean age of the EVAR patients included in the EVAR-1 trial[143] is relatively high (74.1±6.1) and thus the impact of radiation on the incremental costs and effects will probably be negligible.

Since a lifetime time horizon is proposed, short term clinical data from clinical studies need to be extrapolated to capture all differences in costs and effects between treatments. Crucial assumptions concerning survival have to be made when data is lacking. Brown et al.[143] estimated the cost-effectiveness of EVAR compared with OSR and assumed in the base-case analysis that there is no difference in the rate of AAA deaths between treatments after eight years since the risk of AAA death diminishes over time. Chambers et al.[183] used a constant hazard ratio (1.072) for

non-aneurysm related death for EVAR versus OSR until the non-aneurysm related survival curves converged. The impact of these assumptions on the cost-effectiveness needs to be explored through sensitivity analyses.

Table 8.1 | Cost data required for the cost-effectiveness analysis

Category	Resource use	Unit costs
Procedure[a]		
Preoperative embolization		p/procedure
Cardiopulmonary bypass and reperfusion		p/procedure
Theatre time	min	p/min
Preoperative stay	days	p/day
Intensive care unit stay	days	p/day
High dependency unit stay / coronary care unit	days	p/day
Ward stay	days	p/day
Red blood cell	units	p/unit
Platelets	units	p/unit
Fresh frozen plasma	units	p/unit
Fluoroscopic time	min	p/min
Contrast	ml	p/ml
Device & consumables		actual & list prices
Medication use		
Statins	mg	p/mg
Antiplatelet	mg	p/mg
Anticoagulant	mg	p/mg
Betablocker	mg	p/mg
Antihypertensive	mg	p/mg
Follow-up[b]		
Outpatient visits	number of visits	p/visit
CT-scan	number of scans	p/scan
Complications[c]		
Intensive care unit stay	days	p/day
High dependency unit stay	days	p/day
Ward stay	days	p/day
Outpatient visit	visits	p/visit
Emergency room visit	visits	p/visit
Procedures[d]		p/procedure

[a] Primary intervention, conversions to OSR and reinterventions. Including complications during primary admission; [b] 1 year and subsequent years; [c] Cardiovascular complications, renal complications, pulmonary complications, neurological complications. The resource use should be measured of each complication separately; [d] This will depend on the complication

Costs

For the short-term model is it important that valid resource use estimates (e.g. theatre time or blood products) of the procedures are used. Table 8.1 shows the resource use and unit costs that at least need to be collected.

Tables 8.2 and 8.3 present estimates of some of the key parameters identified in Table 8.1. This overview is based on five clinical studies that were identified in the clinical effectiveness review but were excluded based on study design due to selective treatment assignment[13]. Thus, it is crucial to realize that these values should not be used for the economic model without adjustments; instead, they should be seen as indicative for which parameters might differ between treatments.

Table 8.2 | Estimates of key parameters to estimate the costs of OSR

Parameter	min	max	mean	Source
Mean theatre time (min)	89	150	120	178,186
Median theatre time (min)			235	176
Mean blood loss (mL)			3436	177
Median blood loss (mL)	1550	2000	1775	176,186
Mean stay (days)	7.2	21.7	14.0	177,178,186
Median stay (days)			12	176
Mean ICU stay (days)	7.4	29.3	18.3	176,177
Median ICU stay (days)			28	176,178

ICU: intensive care unit

Outcomes

The outcomes of interest for the model are life years (LY) and quality adjusted life years (QALY). LYs are directly estimated with the model using the number of years that patients live after each intervention. Then LYs should be combined with quality of life (QoL) estimates to obtain the number of QALYs for each intervention. It is important to obtain QoL estimates of patients treated with fEVAR/bEVAR, OSR or with no surgery in order to assess differences in QALYs between a minimal invasive procedure (fEVAR/bEVAR) versus an invasive procedure (OSR) and also to compare fEVAR/bEVAR with no procedure. Quality of life was measured with the EQ-5D alongside the EVAR-1 and 2 trials[181,182] (Tables 8.4 and 8.5). These values might also be appropriate for patients with JRAAA or TAAA since it is likely that these patients have the same quality of life as patients with AAA.

2.4 | Analyses

The last step is to actually perform the analyses when the model is populated. Since populating the model for all parameters was not possible, it was not possible to conduct this last step of the assessment phase.

The base-case analysis should report the (incremental) cost-effectiveness of fEVAR/bEVAR versus OSR and fEVAR/bEVAR versus no surgery in both disaggregated and aggregated forms.

In addition, subgroup and sensitivity analyses should be performed. The impact of parameters such as the costs of the endovascular procedures and 30-day mortality on the cost-effectiveness of fEVAR or bEVAR should be evaluated in univariate sensitivity analyses. Scenario analyses estimating the influence of late non-aneurysm mortality, late aneurysm mortality, and complication estimates on the cost-effectiveness should be performed. Furthermore, it could be useful to conduct best-case and worse-case scenario analyses and to produce tornado diagrams. Probabilistic sensitivity analysis should be performed to estimate the influence of parameter uncertainty on the ICER. Cost-effectiveness acceptability curves could be very informative. Lastly, structural uncertainty should be addressed by varying structural assumptions (e.g. disease progression of patients who are converted from fEVAR/bEVAR to OSR).

Table 8.3 | Estimates of key parameters to estimate the costs of fEVAR/bEVAR

Parameter	min	max	mean	Source
Mean theatre time (min)	266	290	278	178,186
Median theatre time (min)			300	176
Mean blood loss (mL)			370	177
Median blood loss (mL)	500	1250	875	176,186
Mean fluroscopy time (min)	54	88	71	178,186
Mean contrast (ml)	156	288	222	178,186
Mean stay (days)	3.5	10.5	7.2	177,178,186
Median stay (days)			7	176
Mean ICU stay (days)	0.9	6.2	3.6	176,177
Median ICU stay (days)			4	176

ICU: intensive care unit

Table 8.4 | Quality of life estimates (EQ-5D) EVAR-1 trial[181]

Timepoint	*EVAR (N=543)*			*OSR (N=539)*		
	mean	**SD**	**N**	**mean**	**SD**	**N**
Baseline	0.75	0.22	541	0.74	0.23	531
0–3 months*	0.73	0.21	238	0.67	0.25	245
3–12 months*	0.71	0.25	476	0.73	0.23	414
12–24 months*	0.74	0.24	398	0.75	0.25	371

* Post-operative

Table 8.5 | Quality of life estimates (EQ-5D) EVAR-2 trial[182]

Timepoint	*EVAR (N=166)*			*No surgery (N=172)*		
	mean	**SD**	**N**	**mean**	**SD**	**N**
Baseline	0.58	0.31	164	0.63	0.28	171
0–3 months*	0.57	0.28	48	0.56	0.29	92
3–12 months*	0.64	0.28	122	0.60	0.26	120
12–24 months*	0.65	0.24	88	0.60	0.30	68

* Post-operative

DISCUSSION

This study presented the first two phases of the appraisal of fEVAR/bEVAR; framing and assessment. The framework of the study, framing phase, is described in this study. Patients diagnosed with JRAAA or TAAA could be treated with fEVAR/bEVAR, OSR or no surgery depending whether they are fit for OSR or not. All interventional treatments are associated with complications such as reinterventions, MI or stroke. Of the four steps of the assessment phase we were able to conduct only the first two steps: 1) performing systematic reviews of the clinical effectiveness and the cost-effectiveness of fEVAR/bEVAR and 2) producing the structure for a decision model. Both reviews resulted in zero included studies. A model structure was proposed based on a previously published report on the cost-effectiveness of EVAR[183]. The last two steps, populating the model and performing the analyses, could not be completed for several reasons: 1) evidence on clinical effectiveness of the interventions is lacking, 2) large variation in technical features of the fEVAR/bEVAR stent grafts and consequent variation in the effectiveness and costs across the stent grafts and patients, making expert solicitation problematic, and 3) fEVAR/bEVAR intervention is an evolving area and consequently the results will not be valid for the near future. However, recommendations on populating the model and on the analyses that can be performed are provided in this study. Furthermore, the type of data that need to be collected are described.

The cost-effectiveness of fEVAR/bEVAR could not be estimated since no evidence on efficacy and costs were available and therefore it remains uncertain whether the extra cost of fEVAR/bEVAR compared with the alternatives is justified by the advantages for patients. Some health economist would argue that it is always possible to model the cost-effectiveness of an intervention since uncertainty analyses can be performed. Univariate and multivariate sensitivity analyses or threshold analyses are appropriate methods to estimate the impact of parameter uncertainty on the cost-effectiveness; however in this specific case, in our opinion, too many parameters were uncertain making these types of analyses less worthwhile. Value of information analyses, estimating the expected value of perfect information for a model, specific parameters or sets of parameters[187], could have been performed although it is very clear that more evidence on efficacy and costs is required. Despite the fact that it is important to perform a CEA, we are of the opinion that no meaningful conclusions can be drawn from such a model other than that more research is required to collect data to inform the model which is already clear without filling the model with arbitrary input values.

Research priorities

Given that there is clearly crucial uncertainty in many input parameters, including probability of technical success (target vessel perfusion), risk of death, durability (risk of relapse), risk of adverse events and quality of life, there is a need for an RCT, or at least a well-conducted prospective cohort study with proper comparability at baseline and statistical techniques to adjust for potential confounding. Also, we recommend that this should be at least in the population of younger, fitter patients, i.e. those for whom OSR is suitable, in order to answer the question whether fEVAR or bEVAR is clinically effective or cost-effective in comparison with OSR. Ideally, there should also be one RCT for each of fEVAR and bEVAR and consideration should also be given to separate trials in the non-OSR eligible population. Preferably, such a trial should be long enough to identify patients who develop longer-term problems such as renal failure.

When considering an RCT evaluating fEVAR/bEVAR, Canavati et al.[176] have identified that it can be a challenge to include a sufficient number of patients so that subgroup analyses with enough statistical power can be performed. Subgroup analyses are important as there will be large variation in both procedures but especially in open procedures for this indication leading to variation in operative risk. Greenberg et al.[188] have also raised the challenge of including sufficient patients. We therefore recommend a multicentre study. However, Greenberg et al.[188] also recognised the challenge of disseminating endovascular skills and the rapid technology improvements that occur for branched devices. It is important to keep in mind that a learning effect can exist and this can negatively influence the perioperative mortality of these procedures. Verhoeven et al.[189] have recognised this problem and suggested that a learning curve has to be taken into account because half of the occlusions in non-stented fenestrations or scallops occurred in fEVAR interventions that were performed in the early stage. Therefore, we

recommend strict criteria in terms of surgeon experience, centre experience (e.g. 50 fEVAR and/or 25 bEVAR procedures in the last 3 years), type of stent graft and OSR technique. Also, a 'tracker trial', i.e. one where the intervention is allowed to change with improvements in technology, might be considered[190]. Ideally, subgroup analyses could also be undertaken to investigate the effect of risks such as aneurysm size and presence of comorbidities.

In addition, we recommend that the CEA should be conducted alongside the RCT or other prospective cohort study. Ideally, in order to take into account both the short- and long-term economic consequences, this ought to be constructed as a model as described in the result section. Furthermore, in designing the prospective study, there is the opportunity to collect primary data to inform such a model, such as resource use and utilities, as specified in detail in the result section. When such a trial is conducted the presented structure can be used to estimate the cost-effectiveness of fEVAR/bEVAR.

Conclusion

Given that not all steps of the assessment phase could be conducted, it remains uncertain whether fEVAR or bEVAR are cost-effective. However, this study gives a clear model structure that can be used to inform decisions about which data should be collected, and can be a first step in the development of a final model once data collection has taken place.


Challenges
Modelling
Cardiovascular
Technologies
Tests
Devices
QALY
ICER
Analyses
Cost-effectiveness
Disease
Markov
Blood
Data
Results
Extrapolating
Costs
CAD
CVD
Thesis
Specificity
Sensitivity Analyses
Guidelines
Angina
EVAR
RCT
PCI
Risks
Drugs
Scenario Analyses
Diagnosis
Structure
Prevention
Intervention
Follow-up
Precision
Validity
Bias
CT-scanner
Survival
TAVI
Frequency
Interaction
Decision Tree
Prior Likelihood
ICA
Stroke
Literature
Efficacy
Persistence
Learning Curve
Gold Standard
Recommendations
Importance
Accuracy
Synergy
Outcomes
Clinical
Regression
Statin
Fevar
False Negative
False Positive
True Negative
Care Pathway
Prevalence
Real-world
Short Term
Observational
Review
Probabilities
Systolic
Diastolic
Ischemic
Cerebrovascular
Technologies
QoL
AAA
Artery
Heart
Surgical
Bevar
DES
Monitoring
Limitations
Indication
Statistics

Chapter 9

Challenges in modelling the cost effectiveness of various interventions for cardiovascular disease

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Pharmacoeconomics. 2014 Jul;32(7):627-37

ABSTRACT

Objectives: Decision analytic modelling is essential in performing cost-effectiveness analyses (CEAs) of interventions in cardiovascular disease (CVD). However, modelling inherently poses challenges that need to be dealt with since models always represent a simplification of reality. The aim of this study was to identify and explore the challenges in modelling CVD interventions.

Methods: A document analysis was performed of 40 model-based CEAs of CVD interventions published in high-impact journals. We analysed the systematically selected papers to identify challenges per type of intervention (test, non-drug, drug, disease management programme, and public health intervention), and a questionnaire was sent to the corresponding authors to obtain a more thorough overview. Ideas for possible solutions for the challenges were based on the papers, responses, modelling guidelines, and other sources.

Results: The systematic literature search identified 1,720 potentially relevant articles. Forty authors were identified after screening the most recent 294 papers. Besides the challenge of lack of data, the challenges encountered in the review suggest that it was difficult to obtain a sufficiently valid and accurate cost-effectiveness estimate, mainly due to lack of data or extrapolating from intermediate outcomes. Despite the low response rate of the questionnaire, it confirmed our results.

Conclusions: This combination of a review and a survey showed examples of CVD modelling challenges found in studies published in high-impact journals. Modelling guidelines do not provide sufficient guidance in resolving all challenges. Some of the reported challenges are specific to the type of intervention and disease, while some are independent of intervention and disease.

INTRODUCTION

Decision analytic modelling when performing economic evaluations of interventions in cardiovascular disease (CVD) is challenging. For example, modelling is necessary if extrapolation of short-term or intermediate results to long-term outcomes is required and numerous strategies need to be evaluated without direct evidence. Thus, modelling inherently poses challenges that need to be dealt with since models always represent a simplification of reality. The presence of challenges could be dependent on the type of intervention or the phase of disease in which the intervention would be used.

There are several ways to deal with the challenges in obtaining an accurate, precise and valid estimate of the cost-effectiveness. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM) have recently published a series of recommendations for best practice in performing cost-effectiveness analyses based on a model[132,187,191-195]. These recommendations suggest some practical solutions to present challenges in modelling. However, these recommendations are not specific for any type of disease or intervention and therefore this review aims to identify and analyse challenges (e.g. multiple indications) in modelling the cost-effectiveness of CVD-interventions that currently exist in the field. Furthermore, we present ways to address the challenges based on current economic modelling guidelines and the opinions of experts from the field.

METHODS

In order to identify current challenges in the field of CVD, a document analysis was performed of model-based cost-effectiveness analyses (CEA) of CVD-interventions that were recently published (ever since January 2009) in disease specific, health economical and general medical journals. In addition, a questionnaire was sent to the corresponding authors of the selected papers to obtain a more thorough overview of current CVD-modelling challenges.

Selection

To select systematically relevant papers, we used a search string that contained both cost-effectiveness terms, based on the validated NHS-EED cost-effectiveness filter[196], and a disease specific MeSH term ('cardiovascular disease').The search was performed on May 8, 2013. We assumed that the papers published in journals with a relatively high impact factor are more susceptible to complicated challenges. Therefore, we limited the search results to twelve relatively high impact factor journals in 3 categories: cardiovascular medicine, general medicine and health economics/health technology assessment (HTA) journal. To select these twelve journals we sorted all possible journals per category on impact factor, based on journal citation reports®[197]

and included the four highest ranked journals that also published sufficient cardiovascular CEAs. The following journals were selected in the cardiovascular medicine category: Circulation, European Heart Journal, Journal of the American College of Cardiology, and International Journal of Cardiology; in the general medicine category: The Lancet, New England Journal of Medicine, The Journal of the American Medical Association, and Annals of Internal Medicine; and in the health economical category: Value in Health, PharmacoEconomics, Health Technology Assessment, and Medical Decision Making.

We sorted the search results (via Ovid MEDLINE®) of the twelve journals on entry date and selected the most recent CEAs or methodological papers presenting results, both based on modelling methods and evaluating a CVD-related intervention, until we reached a convenience sample of 40 unique corresponding authors. Authors were selected if they met the following inclusion criteria: they should have evaluated a CVD intervention using modelling methods and could only be included once as a corresponding author. The most recent publication of authors that met inclusion criteria was included.

Document analysis

Using the 40 publications, we extracted CVD modelling challenges explicitly mentioned in the methods and discussion sections of the papers and determined the frequency of these challenges over all papers. Before data extraction, a list with challenges was created to identify possible challenges that were present in the studies. These challenges were based on our own experience and that of five other researchers with sufficient experience (3–15 years) in performing model-based CEAs. A challenge was added to the list when it was described in the paper but not included in the existing list. For each paper, two reviewers (LB and WR or JS) identified the challenges described in the methods and discussion sections. To be complete, we included the identified challenges of both reviewers after we carefully considered both sets of results. Challenges were initially analysed by type of intervention, although it is likely that challenges are not specific for one type of intervention and therefore present in several interventions. Interventions were categorised into tests (e.g. screening, diagnostic), non-drug interventions (e.g. surgically or non-diagnostic devices), drug interventions, disease management programs (DMPs) and public health interventions.

Questionnaire

To supplement our literature review, we sent a questionnaire by e-mail to the corresponding authors of the 40 papers to identify challenges that were not described in the papers and to estimate the importance of the challenges. The same five modelling experts tested a pilot version of the questionnaire and indicated new challenges that were not previously identified. The first part of the questionnaire focussed on the solved and unsolved challenges that authors faced while creating and using the model used to perform their analyses. Authors were asked to provide

data requirement and modelling challenges and also asked to provide their source of inspiration if they managed to solve the specific challenge. The second part of the questionnaire focussed on the challenges that the respondent may have experienced during any CEA modelling of a CVD intervention. The list used for the document analysis was also the basis for the questionnaire. Respondents were asked to indicate how often the challenge had occurred in model based CVD intervention CEAs conducted by the respondent and how much impact it could have had on the ICER.

Analysis

The challenges brought forward by the corresponding authors and identified in the literature review were analysed. We then examined ways to address them based on the current modelling guidelines[132,187,191-195], other literature and the solutions provided by the authors.

RESULTS

Selection

The systematic literature search identified 1720 potentially relevant publications. In order to reach the target of 40 relevant papers with unique corresponding authors, we read title, abstract and full paper in case title and abstract were non-conclusive, of 294 publications (Figure 9.1). Table 9.1 provides an overview of the publications written by these authors. Most (49%) of the publications involved CEAs of tests and drugs; analyses of non-drug interventions, disease management programs and public health interventions were less common. Health economics journals accounted for approximately half of the publications included in this study.

Challenges

Table 9.2 presents the presence and frequency of each challenge in each type of intervention and provides ways to address them. Furthermore, papers that have presented a solution for a specific challenge are also identified in Table 9.2.

Data requirements challenges

Challenges such as lack of data (e.g. effectiveness, costs, adverse events or parameter distributions) and difficulties in evidence synthesis are usually addressed by performing sensitivity analyses which show the impact on the outcomes. Univariate or multivariate sensitivity analyses, scenario analyses or probabilistic sensitivity analyses are often used in addressing data requirements challenges. Furthermore, it is important to recognize the problem of publication bias when a meta-analysis is performed to estimate the effectiveness of an intervention. Trial registries (e.g. ClinicalTrials.gov) can be searched to identify clinical trials that have not published their results to reduce the risk of bias from selective publication. Furthermore, funnel plots can be used to

identify if publication bias exists[198]. When publication bias is an issue then it could be useful to adjust for this in the meta-analysis[199].

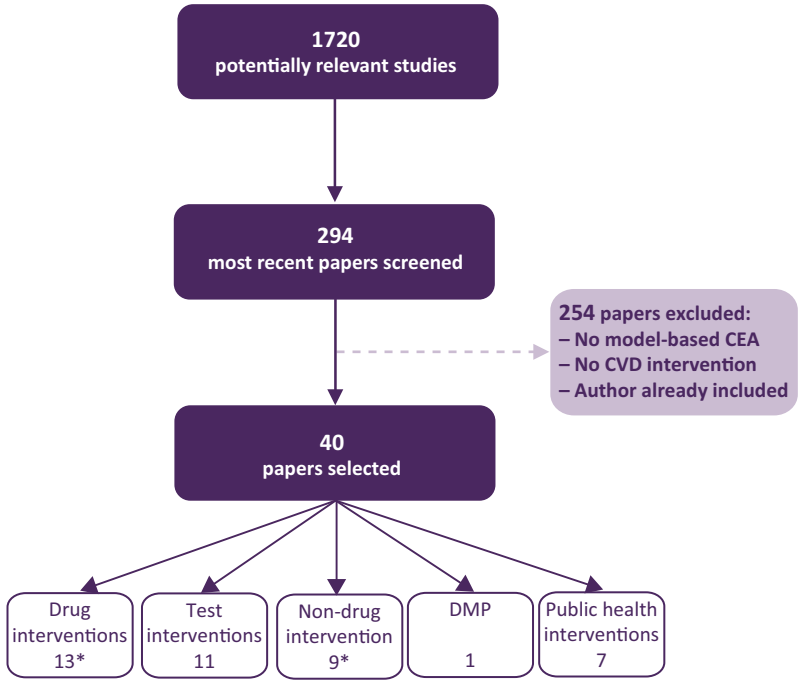

Figure 9.1 | Flowchart of selected papers

* One study investigated two types of interventions (drug and non-drug interventions)

Structural uncertainty

Besides parameter uncertainty our document analysis showed that modelling studies often encountered structural uncertainties. This means that it was difficult to include or consider: i) all relevant comparators, ii) all relevant disease states or events, and iii) a sufficient time horizon to capture all relevant differences in costs and consequences. Often not all relevant comparators are included in the model due to data requirements as could be seen in the study performed by Magnusson et al.[200] which estimated the cost-effectiveness of drug-eluting stents compared with coronary artery bypass based on the FREEDOM trial. The trial did not include the second generation of drug-eluting stents, which meant that the authors were unable to evaluate stents that were available during the trial. When direct evidence between comparators is lacking then mixed treatment comparison or network meta-analysis could be a solution. Recently, seven tutorial papers were published on evidence synthesis methods for decision making including network meta-analysis[201-207]. Stettler et al.[208] compared the safety and effectiveness of bare metal

stents and drug-eluting stents by means of a network meta-analysis. Bojke et al.[209] discussed ways (modelling averaging, model selection and parameterizing structural uncertainty) to address structural uncertainty. Frederix et al.[210] have explored the influence of model structures in breast cancer treatment on the estimated cost-effectiveness of an intervention.

Table 9.1 | Characteristics of the studies included in the literature review

	Frequency Intervention strategy[a]										
	Test		Drug		Non-drug		DMP		Public health intervention		
	N	%	N	%	N	%	N	%	N	%	Total
Generic journals	**1**	**17%**	**1**	**17%**	**0**	**0%**	**0**	**0%**	**4**	**67%**	**6**
The Lancet	1	50%							1	50%	2
New England Journal of Medicine									1	100%	*1*
Annals of internal medicine			1	33%					2	67%	*3*
Journal of the American Medical Association											*0*
Cardiovascular disease journals	**5**	**33%**	**4**	**27%**	**4**	**27%**	**0**	**0%**	**2**	**13%**	**15**
European Heart Journal					1	100%					*1*
Circulation	3	43%	2	29%	1	14%			1	*14%*	*7*
Journal of the American College of Cardiology	2	50%			1	25%			1	*25%*	*4*
International Journal of Cardiology			2	67%	1	33%					*3*
Economic evaluation journals	**5**	**25%**	**8**	**40%**	**5**	**25%**	**1**	**5%**	**1**	**5%**	**20**
Health Technology Assessment	1	33%			1	33%			1	33%	*3*
Medical Decision Making			1	100%							*1*
Value in Health	3	21%	6	43%	4	29%	1	7%			*14*
PharmacoEconomics	1	50%	1	50%							*2*
Total	11	*27%*	13	*32%*	9	*22%*	1	*2%*	7	*17%*	41

DMP: disease management programme

[a] One study investigated two types of interventions (drug and non-drug interventions)

Table 9.2 | Frequencies of challenges per type of interventions

	Test intervention (N=11)		Non-drug intervention (N=9)		Drug intervention (N=13)		DMP (N=1)		Public health intervention (N=7)		Total (n=41†)		Methodological paper	Example paper
Data requirement challenges	#	%	#	%	#	%	#	%	#	%	#	%	reference	reference
1 Treatment effectiveness	8	73%	8	89%	10	77%	1	100%	5	71%	32	80%	191,199,211	
2 Prevalence	2	18%	NA	NA	NA	NA	NA	NA	3	43%	5	31%	191,211	
3 Accuracy data	5	45%	NA	NA	NA	NA	NA	NA	4	57%	9	56%	191,211212	
4 Compliance*	3	27%	1	11%	5	38%	1	100%	1	14%	11	37%	191,211	213
5 Quality of life	7	64%	8	89%	7	54%	0	0%	3	43%	24	71%	191,211	
6 Resource use	6	55%	7	78%	7	54%	1	100%	3	43%	24	60%	191,211	
7 Unit costs	6	55%	5	56%	9	69%	0	0%	4	57%	23	56%	191,211	
8 Indirect costs	1	9%	1	11%	0	0%	0	0%	0	0%	2	5%	214	
9 Missing values	1	9%	4	44%	0	0%	0	0%	0	0%	5	13%	215	
10 Parameter distributions	4	36%	4	44%	3	23%	1	100%	2	29%	14	35%	191,211,216	
11 Adverse events	5	45%	6	67%	6	46%	0	0%	1	14%	18	45%		
12 Subpopulation data	4	36%	1	11%	2	15%	0	0%	2	29%	8	20%	217	
13 Evidence synthesis	1	9%	3	33%	5	38%	0	0%	1	14%	10	25%	132,187,192,201	218
Modelling challenges	#	%	#	%	#	%	#	%	#	%	#	%	reference	reference
1 Structure	3	27%	4	44%	3	23%	0	0%	4	57%	13	32%	209,210	
1a Comparators	3	27%	3	33%	0	0%	0	0%	0	0%	6	15%	191,201	208,219
1b Disease pathway	2	18%	2	22%	0	0%	0	0%	2	29%	6	15%	132,220	150
1c Time horizon	0	0%	1	11%	1	8%	0	0%	0	0%	2	5%	191,192,221	90
2 Heterogeneity	2	18%	0	0%	2	15%	0	0%	0	0%	4	10%	211,217	
3 History	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	191	

Table 9.2 | *(Continued)*

		Test intervention (N=11)		Non-drug intervention (N=9)		Drug intervention (N=13)		DMP (N=1)		Public health intervention (N=7)		Total (n=41†)		Methodological paper	Example paper
4	Extrapolating short/intermediate results	7	64%	7	78%	7	54%	1	100%	4	57%	26	65%	191	222
5	Competing risks	2	18%	0	0%	1	8%	0	0%	0	0%	3	8%	223	224
6	Multiple testing	3	27%	0	0%	NA	0%	NA	0%	2	29%	5	31%	225,226	
7	Multiple interventions effects	0	0%	1	11%	0	0%	0	0%	2	29%	3	8%		227
8	Learning curve	2	18%	0	0%	NA	NA	NA	NA	0	0%	2	8%	228	229
9	Wait time (e.g. capacity constraints)	0	0%	2	22%	NA	NA	NA	NA	0	0%	2	8%	230	125
10	Multiple indications	0	0%	0	0%	0	0%	0	0%	1	14%	1	3%	231	
11	Lead time	0	0%	NA	NA	0	0%	0	0%	0	0%	0	0%	232	
12	Reusability	NA	NA	0	0%	NA	NA	NA	NA	NA	NA	0	0%	233	
13	Process utilities	NA	NA	0	0%	NA	NA	NA	NA	NA	NA	0	0%	233	
14	Scenario analyses	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%		

* Compliance in studies that evaluate test interventions applies to the drug treatment, which is part of the strategy
† One study investigated two types of interventions (drug and non-drug interventions). NA = not applicable.
The proportions were calculated based on the number of studies that could have been exposed to the challenges.

Patient heterogeneity

The difficulty of incorporating patient heterogeneity is reported in some of the papers. Sufficient incorporation of heterogeneity in a model requires a great deal of data that is often not available. Recently, a review by Grutters et al.[217] provided a comprehensive overview of the current knowledge regarding patient heterogeneity within economic evaluations of healthcare programs and provided guidance for researchers to address heterogeneity.

Extrapolation of short term or intermediate results

Modelling guidelines recommend that models should include long term or final outcomes[191]. One common problem in modelling is that the length of follow-up of a clinical study used in the model is shorter than the time horizon of the model. Another problem is the fact that only intermediate outcomes (e.g. sensitivity and specificity of coronary angiography) or surrogate outcomes (e.g. the effect of statins on LDL cholesterol) are presented. Methods to extrapolate intermediate and surrogate outcomes are: i) using population level data (e.g. national mortality statistics), ii) long-term epidemiological (observational) studies or registries that reflect the natural history of disease, iii) extrapolating survival curves, and iv) assuming different scenarios for extrapolation (based on e.g. expert opinion). A common approach in CVD is to use trial-based results (short term) and extrapolate them by using literature or assuming different scenarios for extrapolation. Furthermore, final outcomes (lifetime costs or survival) of previously published models that focus on a later stage in disease progression can be used. For example, Lieu et al.[222] used published results from a modelling study to estimate the cost-effectiveness of primary angioplasty. In addition, a CEA evaluating new generation CT scanners for the diagnosis of coronary artery disease combined five existing models to extrapolate test outcomes[62]. However, combining existing models introduces additional uncertainty since these are often designed for different populations/interventions[234].

Competing risks

Some studies (8%) recognized the challenge of competing risks (events that preclude or alter the likelihood of another event occurring[193]. The paper of Putter et al.[223] reviewed statistical methods for the analysis of competing risks and how to model them. Wolbers et al.[224] has considered three models to account for competing risks in risk prediction models for coronary heart disease.

Multiple intervention effects

Some treatment strategies consist of multiple interventions and some single interventions have an effect on more than one clinical outcome. Estimating the effectiveness of such interventions could be a challenge. It is more likely that CEAs evaluating public health interventions or DMPs have more difficulty in estimating the effectiveness since they often exist of multiple interventions. This challenge can also arise when estimating the cost-effectiveness of lifestyle interventions or drug interventions such as the 'poly pill' that combines several pills (e.g. statins, aspirin, blood

pressure lowering drugs, folic acid)[235]. It is important to recognize the problem of interrelating outcomes and overestimation of the 'real' treatment effect. Interrelating outcomes are present if an intervention (e.g. cardiovascular DMP) has an effect on multiple outcomes (e.g. blood pressure and smoking) which interact in some way to improve health. When it comes to primary CVD prevention, the Framingham risk score[9] or the SCORE risk function[7] are often used to overcome the problem of interrelating outcomes. Both risk functions estimate the risk of developing a (non-) fatal event in the coming ten years based on several risk factors (e.g. smoking, cholesterol or age). While none of the included studies consisted of multiple interventions, some of them recognized that their single intervention could have an effect on more than one clinical outcome. When treatment effectiveness of such a strategy is lacking it is possible to use a synergy factor. Van Kempen et al. multiplied the individual relative risks of the single interventions (aspirin and statins) and multiplied this with a synergy factor [52]. This factor can be varied through sensitivity analyses and incorporates the interaction between drugs (synergy or dyssynergy).

Learning curve

Obtaining effectiveness evidence of new tests and other non-drug interventions (e.g. endovascular aneurysm repair vs. open aneurysm repair) is often difficult due to the presence of a learning curve[231]. It is important to include the consequences of learning effects for new (invasive) procedures. Learning effects could influence operating time of a procedure, diagnostic accuracy, and the frequency of adverse events. Ramsay et al. presents statistical techniques to incorporate learning effects of tests and procedures but concluded that new statistical techniques should be developed[228]. The impact of incorporating a learning curve on the cost-effectiveness of strategies will vary depending on various factors. Woods et al. has investigated the impact of the learning curve of heart transplantation on the operative and post-operative hospital costs[229] .

Waiting time

In real life it is likely that tests and procedures are not performed immediately after each other, sometimes because of capacity issues. However, CEAs usually do not incorporate capacity constraints and the time delay between tests and procedures. Two papers identified waiting time as a challenge[125,143] and one of them examined this issue in detail[125]. Neglecting waiting time may lead to an overestimate of the effectiveness and cost-effectiveness of an intervention, since a delay in assessment may prolong suffering or increase risk of cardiovascular events (e.g. MI or cardiac arrest). If waiting time is deemed important, a disutility for the quality of life loss due to postponed treatment can be added. When the delay in treatment is due to capacity constraints then modelling guidelines suggest using an agent-based simulation model or a discrete-event simulation (DESM) to incorporate competition for resources[191], as performed by Jahn et al.[125] who evaluated the cost-effectiveness of drug-eluting stents versus bare metal stents. A tree that precedes a Markov model can also be used to include waiting time from capacity constraints by modelling a proportion of the cohort that suffers from these constraints.

Multiple indications

Performing an economic evaluation of an intervention that can be used for several indications is also considered as a challenge (3%). Usually interventions are evaluated for a specific indication, however many tests and drugs can be used for several indications. Drugs are divisible and can be evaluated for each indication separately and thus are not per se a challenge. However, for example the cost-effectiveness of a CT scanner in diagnosing CAD can be evaluated but this intervention can also be used in various ways such as brain CT scans. The weighted average of its use in multiple applications can be used to estimate the overall value of both costs and effects of the intervention[231] in order to decide whether or not to purchase the scanner. In order to estimate a weighted average of its use for all applicants we need to know the relative frequency of each application and have a sufficient understanding of the alternative strategy, including the health and economic consequences of correct and incorrect diagnoses. Furthermore, all effects would preferably be expressed using the same unit of health gain (i.e. life years or QALYs).

Diagnostic performance

Several authors (56%) have indicated that it is a challenge to obtain values for the diagnostic accuracy (sensitivity and specificity) of a test. These input parameters to a model usually have an important impact on the cost-effectiveness of the test since these parameters are key in extrapolating an initial disease status assessment, either being correct or incorrect (false positive or false negative diagnosis). It is even more a challenge when tests are performed in combination or sequence and previous test results need to be incorporated in the model, as recognized by Denchev et al.[236]. It is a challenge to estimate the sensitivity and specificity of each individual test and of the whole strategy. It is very common to assume that tests are independent, however this does not allow for already known test results leading to misinterpretation of the test results (posterior probability). Since the interpretation depends on the prior probability (known test results and prevalence of outcome) and the accuracy of the test. Hunink et al. has explored the influence of assuming independence for multiple test strategies[225]. Weintraub et al. examined the application of Bayes theorem in non-invasive diagnosis of CAD[226] and showed that it is not always appropriate to assume independency. This challenge is mainly due to lack of data, since it is almost impossible to perform an observational diagnostic evaluation study in order to derive reliable estimates of diagnostic, therapeutic and health status outcomes for multiple test strategies[237]. Furthermore, estimates of the sensitivity and specificity of a test (e.g. CT angiography) could also be invalid since they are often derived by comparing the result with a “gold standard” (e.g. invasive coronary angiography) which may not necessarily be 100% accurate[62]. When data is not available, the best strategy is to vary the accuracy estimates in sensitivity analyses to estimate the impact on the cost-effectiveness. However, the sensitivity and specificity of a test might be linked, so that improvements in one parameter may be achieved at the expense of reductions in the other[212]. Berry et al.[212] has incorporated the link in a decision tree evaluating magnetic resonance angiography. In addition, the ISPOR-SMDM modelling

guidelines recommend incorporating test results that are prognostic in the states or as tracker variables in state-transition models[192].

Compliance and persistence

Compliance and persistence of interventions (e.g. drug intervention or lifestyle interventions) is usually higher in clinical trials than in daily practice due to close monitoring. Non-compliance can have an impact on medicine acquisition costs and subsequent overall health care resource utilization and costs[238]. However, non-compliance may not always result in clinically meaningful differences between efficacy and effectiveness due to long duration of action in relation to its dosing interval (e.g. statins)[238]. Sokol et al. has investigated the impact of medication adherence on hospitalization risk and healthcare costs for four conditions: hypertension, diabetes, chronic heart failure and hypercholesterolemia[213]. Drummond et al. proposes some suggestions for trials to become more generalizable to a real-world situation[239]. Guidelines on compliance measurements are provided by Peterson et al.[240]. While compliance could also be based on what is seen during observational studies, these must be adjusted for confounding through multivariate regression techniques or propensity scoring[192]. If no 'real' estimates of the compliance are available, it could be useful to perform several scenario analyses with different assumptions to estimate the impact of compliance on the cost-effectiveness[241]. Ideally, these scenarios should be based on expert opinion, partly to determine how any observed short term compliance rates could be extrapolated. Modelling guidelines recommends considering dynamic characteristics like compliance in the states or as tracker variables[187]. Hughes et al.[238] also recognized the challenge of incorporating compliance into models and provided some techniques to implement compliance in decision models, DES models and Markov models.

Other challenges

Other challenges not identified in the document analysis but included in our survey are: i) reusability, ii) lead time bias, iii) incorporating history, iv) process utilities, and v) defining appropriate scenario analyses. Some interventions such as telemonitoring devices for heart failure can be reused in several patients and this element of reusability might be incorporated in economic evaluations[233]. Lead time bias could be present in test interventions in the CVD field[232] and should be considered in CEAs. Incorporating history in a model may be a challenge and could be solved by increasing the number of states in state-transition models or modelling the cost-effectiveness with a DESM model[191]. Process utilities (ease, comfort of use or the unpleasantness of a device) could be a potential challenge, although this was not identified in any of the studies included in the document analysis.

Questionnaire

In total, six (15%) corresponding authors completed and returned the questionnaire after sending one reminder to all corresponding authors and an additional reminder to the authors who were initially willing to complete the questionnaire. Of the six papers they had authored, two focused on drugs, two on tests, one on a population based strategy, and one on a device. These authors had previously conducted an average of four CEAs of CVD interventions using an economic model. The challenges found in the document analysis were confirmed by the respondents, in particular lack of data and extrapolating short term results. However, the questionnaire also led to the identification of challenges that were not described in the paper. For example, one respondent indicated that extrapolation of initial surrogate outcomes to later clinical events was a challenge, even though this issue was not prominently documented in the paper written by that author. This was very likely because it was a methodological paper which focused on the impact of utilities on the incremental effects[242].

DISCUSSION

Model-based cost-effectiveness analyses of CVD interventions are always accompanied by challenges in modelling methods and data requirements. This review identified and analysed the challenges that currently exist in the CVD area. Furthermore, some ways to address the identified challenges based on the literature and on expert opinion are mentioned.

Lack of effectiveness data and quality of life data, determining a model structure, and extrapolating short term or intermediate results are very frequently reported or implied challenges in the document analysis. However, frequency is not necessarily an indicator of importance (i.e. degree of impact on the ICER). Less frequently reported challenges are difficulties in incorporating patient heterogeneity and including waiting time for an intervention in the model. The document analysis also showed that more complex interventions are associated with more and more complex challenges. Public health interventions, DMPs and tests are interventions being more difficult to evaluate since it combines several interventions (e.g. companion diagnostic) instead of one single therapy. CVD interventions have become more complex (including DMP, targeted treatments and devices) over the years, meaning that more parameters and relationships between parameters have to be included in the analysis. Consequently, the complexity of models has also increased over the years[243]; for example, a simple decision tree is now used much less often than before. Despite the increased complexity of models, authors of the included studies did not report any challenges that were impossible to be solved. One solution that is often used to overcome challenges is the use of sensitivity analysis. The influence of structural uncertainty and patient heterogeneity on the outcomes is less often assessed in model-based economic evaluations than uncertainty regarding parameters and methodology.

Limitations

Since we limited our review by including only 40 papers in a limited number of journals, the papers do not represent all model-based CEAs of CVD interventions. However, we do not expect that the challenges identified using the document analysis differ substantially from those reported in other papers since we have used the most recent papers and those who were published in the most relevant and highest impact journals.

The identification of challenges from papers is a subjective process which may result in inconsistencies when estimating their frequencies. However, we tried to eliminate this subjectivity by having two reviewers score all studies. Furthermore, the identification of challenges was dependent on whether authors reported all of the challenges they encountered in their study. Consequently, some of the challenges actually encountered might not have been identified by the reviewers and this might have led to an underestimation of the frequencies. To identify challenges that were not reported in the articles we have sent the questionnaire to the corresponding authors. However, the response rate was 15% and therefore the usefulness of the questionnaire results may be limited. For the responders, the questionnaire did confirm the results of our own document analysis.

Recommendations

This review identified challenges that were present in recently published model-based CEAs in the field of CVD. However, most of these challenges and the ways to address them could also be applied to interventions in other disease areas. Challenges are often the result of data that is not available, particularly relating to CEAs of test and non-drug interventions. To our opinion there are two main reasons for this. First, the current regulatory framework in the US and Europe for tests and non-drug interventions is less stringent than for pharmaceuticals; i.e. the European Medicines Agency does not requires a randomized study design for market approval, while the US Food and Drug Administration requires only a single RCT demonstrating safety and effectiveness for high-risk tests or non-drug interventions[233]. We recommend the regulations concerning pharmaceuticals should be applied to these type of interventions as well since these interventions are also subject to the same budget constraints and should therefore meet the same requirements for appraisal[233,244]. Second, tests and non-drug interventions are generally also associated with clinical research limiting factors such as the impossibility of double blinding. We recommend that primary studies on tests and non-drug interventions pursue using rigid research methods as in drug efficacy studies.

We found that the validity of economic models concerning the challenges and assumptions are often not described in papers. However, if validity of models is described, this generally concerns the face validity and technical validity (debugging) only, instead of disclosing how challenges are addressed. We recommend authors were to report their findings according to the CHEERS

statement [245] making it easier to investigate the validity of the model. While modellers are generally very resourceful when it comes to overcoming challenges, one could question whether those challenges are adequately addressed since there are often many ways to do so. For instance, Van Kempen et al. showed that the use of different methods to model the treatment effectiveness of statins (through lipid level modification, fixed risk reduction of CVD events or risk reduction of CVD events proportional to individual change in low-density lipoprotein cholesterol) led to different results[227]. Consequently, they also addressed the importance of carefully considering the assumptions underlying a simulation model and performing extensive model validation. As in the case of breast cancer modelling[246], we recommend standardization of and better guidance for disease-specific modelling in economic evaluations

Conclusions

Modelling is unavoidable when performing comprehensive economic evaluations and always comes with challenges. This study provides examples of CVD modelling challenges encountered during studies published in high-impact journals. Some of the reported challenges are specific for CVD, but most challenges are present in all types of diseases. Modelling guidelines do not provide sufficient assistance in resolving all challenges but it is probably unrealistic to expect this. Besides identifying where more research is needed, this review provides some directions for researchers about how to deal with modelling challenges when performing cost-effectiveness analyses in the area of cardiovascular disease.

Challenges
Modelling
Tests
Devices
Cardiovascular
Technologies
Analyses
QALY
ICER
Markov
Data
Results
Blood
Cost-effectiveness
Disease
Costs
CVD
PCI
CAD
Extrapolating
Intervention
Diagnosis
Prevention
Thesis
Specificity
Sensitivity Analyses
Scenario Analyses
Drugs
Risks
EVAR
Guidelines
Angina
Follow-up
Literature
Precision
Identification
Validity
Bias
Survival
TAVI
Structure
RCT
Review
Observational
Gold Standard
False Negative
False Positive
True Negative
True Positive
Decision Tree
Prior Likelihood
Frequency
Perspective
Learning Curve
Persistence
Efficacy
Stroke
Diastolic
Systolic
Recommendations
Statin
Accuracy
Synergy
CT-scanner
Importance
Interaction
Monitoring
Statistics
ICA
Short Term
Probabilities
Outcomes
Technologies
Care Pathway
Real-world
Prevalence
Prognostic
Fevar
Bevar
Stenosis
CABG
Artery
Surgical
Heart
Thrombosis
Regression
Clinical
Compliance
Relative Risk
Transition
Indication
Limitations
Budget
Methods
Document Analysis
Plaque
Cerebrovascular
Ischemic
Balloon
Wait Time
Treatment
Simplification
Impact
Effectiveness
Bypass

Chapter 10

Discussion

Since healthcare expenditures are expected to rise in the future due to aging and the development of new medical technologies, it is necessary to spend the healthcare budget wisely. Cost-effectiveness analyses can improve the quality of choices in allocating limited health care resources. Cardiovascular disease (CVD) accounts for 9.2% of the total health care expenditure in the Netherlands [2]. In this area many non-pharmaceutical technologies (e.g. stents, prostheses and diagnostic tests) are used to diagnose and treat patients with CVD. In the previous years, many new or improved non-pharmaceutical technologies came to the market and therefore it is important to estimate if these interventions are cost-effective compared to existing interventions. However, it is often challenging to accurately estimate the cost-effectiveness of these interventions due to a number of reasons.

In this thesis, the aim was to assess the cost-effectiveness of various technologies in CVD and to identify and deal with challenges in the cost-effectiveness analysis methods. The cost-effectiveness of a hypothetical test for primary prevention of CVD was estimated. We evaluated the cost-effectiveness of diagnostic tests for primary and secondary prevention of coronary artery disease (CAD) and the cost-effectiveness of drug-eluting stents (DES) versus bare metal stents (BMS) was summarized in a systematic review. Treatment variation (stent choice) in patients diagnosed with CAD and the health related quality of life (HRQoL) of patients with CAD were explored. Subsequently, the cost-effectiveness of fenestrated endovascular repair (fEVAR), branched endovascular repair (bEVAR) and endovascular repair (EVAR) versus open surgical repair (OSR) or medication was estimated. Finally, we described the challenges that arise in modelling the cost-effectiveness of CVD interventions in a review paper.

OVERVIEW OF CASE STUDIES

In **Chapter 2** we estimated the potential cost-effectiveness of a biomarker test that could be used to decide which individuals with an intermediate CVD risk would benefit from statin treatment. Prognosis of different age- and gender-specific cohorts was simulated with a Markov model to estimate the potential costs and quality-adjusted life-years for four strategies: treat all with statins, treat none with statins, treat according to the European guidelines, or use a test to select individuals for statin treatment. We concluded that a perfect hypothetical test would dominate the other strategies if the test did not cost more than €237, consequently a less-than-perfect test would have to cost less than €237.

New generation dual-source coronary CT (NGCCT) scanners were evaluated in **Chapter 3** for patients with known or suspected CAD who are difficult to image. The cost-effectiveness was assessed for three strategies: use of invasive angiography (ICA) only, ii) use of NGCCT only, and iii) use of a combination of NGCCT and (in the event of positive NGCCT) ICA. Extensive modelling, combining several models, was performed to estimate the cost-effectiveness of NGCCT for both CAD populations, separately. We concluded that the use of NGCCT might be considered as cost-effective in both populations since it is cost-saving compared to ICA and it generates similar health effects.

In **Chapter 4** we explored what factors are associated with variation in stent choice in patients undergoing a percutaneous coronary intervention (PCI), based on a prospective cohort of Dutch patients with (un)stable CAD treated with BMS or DES. Using multiple logistic regression analyses we showed that besides clinical factors, which may be considered as legitimate reasons for variation, the treating hospital was also associated with type of stent. This association with stent choice could arise because of financial arrangements with stent manufacturers, budget constraints or operators preferences (believers versus non-believers of DES) which may lead to differences in long-term outcomes.

In **Chapter 5** we performed multiple linear regressions to identify variables that are significantly associated with HRQoL and SF-36 component scores in Dutch patients with stable and unstable CAD. We observed significant associations with gender, systolic blood pressure, body mass index, previous PCI, New York Heart Association class, previous cerebrovascular accident or transient ischaemic attack, peripheral vascular disease, pack-years (tobacco) and pulmonary disease in the stable CAD group. Unstable CAD patients had higher average physical component score, mental component score and SF-36 dimension scores than stable CAD patients. The mental health dimension was the least affected dimension of the SF-36 but CAD had a negative impact on the physical dimensions. Knowledge of these associations can help to identify ways to improve care (e.g. increase physical activity) and thereby improve HRQoL.

In **Chapter 6** we presented a case study, a systematic review on the cost-effectiveness of DES versus BMS using meta-regression analyses exploring the usefulness of such methods compared with conventional review methods. Sixteen eligible studies were identified, with a combined total of 508 analyses, and the incremental cost-effectiveness ratios found in these studies ranged from DES being dominated by BMS to DES being dominant. The meta-regressions showed associations (e.g. type of lesion) that were expected (based on individual studies), however we also revealed unpredicted associations: e.g. model quality was negatively associated with the number of repeat revascularizations avoided. Consequently, meta-regressions can be of added value, identifying significant associations that could not be identified using conventional review methods or sensitivity analyses of individual studies.

Patients with a large unruptured abdominal aortic aneurysm (AAA) can be treated electively with EVAR or OSR. An existing model estimating the lifetime cost-effectiveness of EVAR for the UK was adopted for the Netherlands in **Chapter 7**. EVAR and OSR can be considered equally effective and in addition EVAR was cost-saving compared with OSR for a cohort of individuals (87% men) with an age of 72 years old. Thus EVAR can be considered as a cost-effective solution for patients with AAA, however this is highly dependent on the price of an EVAR device and the degree to which EVAR reduces hospital days, complications and 30-day mortality.

Besides estimating the cost-effectiveness of EVAR versus OSR we described the cost-effectiveness of fEVAR and bEVAR in **Chapter 8**. This study was performed as a short report for National Institute for Health Research Health Technology Assessment programme and followed two phases (framing and assessment). The assessment phase was performed according to the NICE guidelines on technology appraisal methods and has four steps: literature reviews of (cost-) effectiveness, design of mathematical model, inclusion of data in model, and analysis. We showed that the framing phase and the first two steps of the assessment phase could be performed. However, we were unable to populate the model and estimate the cost-effectiveness of fEVAR/bEVAR since no evidence on efficacy and costs were available. It therefore remains uncertain whether the extra cost of fEVAR/bEVAR is justified by the advantages for patients.

CHALLENGES ENCOUNTERED AND DEALT WITH IN THE CASE STUDIES

Modelling methods to estimate the cost-effectiveness of cardiovascular interventions require some simplification of reality. It is impossible to develop a model that estimates the (incremental) cost, (incremental) effects and disease progression both accurately and validly without making assumptions. As a consequence, we also encountered many challenges in the case studies described in chapters 2–8; some of these could be dealt with, while some could not.

The main challenge of almost all economic evaluations is lack of data, although the degree of missing data varies between studies. The type of lack of data is dependent on the timing of the economic evaluation (Figure 10.1). When an economic evaluation is performed while research is still focusing on basic research of the mechanisms there is often no data about the technology being developed that can be used in an economic evaluation. For example, in **Chapter 2** the aim was to estimate the cost-effectiveness of a hypothetical test to support decisions about statin treatment and, like many other early HTA studies, there was no accuracy and cost data about the test. Therefore, we were required to perform sensitivity analyses and scenario analyses to estimate the potential cost-effectiveness of the test. Although it could be argued that this cost-effectiveness analysis was performed too early, sensitivity analyses enable us to determine the parameters of the test that were required in order for it to be cost-effective. The second type of lack of data exists before a product enters the market but has been investigated in several studies (e.g. RCT) which are needed for market approval. When data from these studies is used in a cost-effectiveness analysis of that product, the generalizability to the real world is limited due to the strict inclusion and exclusion criteria used in creating the study population. This type is often present for pharmaceutical interventions, since non-pharmaceutical interventions may not be required to estimate the effectiveness of the intervention in a randomized clinical study. The last type of lack of data was present in **Chapter 7** where we estimated the cost-effectiveness of EVAR. EVAR was already used in daily practice and thus clinical data was available since the EVAR-1[137], OPEN[138] and ACE[139] trials were published. However the data presented in the clinical trials were 'outdated' meaning that daily practice cannot be compared with the care that was provided at the time that the trials were conducted. Nowadays, the frequency of complications and length of stay after EVAR have decreased over time as a result of technological advances and the increasing experience (learning curve) with the procedure. These types of temporal changes in effectiveness, safety and efficiency are often seen in non-pharmaceutical technologies due to their short product lifecycle. Consequently, other sources of clinical data (DSAA registry) were required to obtain a valid and relevant cost-effectiveness estimate since it is unlikely that a new RCT will be conducted due to ethical reasons.

Estimating the cost-effectiveness of a test (e.g. diagnostic) requires more complex modelling than that of pharmaceuticals since test strategies have an effect on the treatment pathway and not directly on the effectiveness[247]. Furthermore, besides the improvements in treatment decisions also the consequences of incorrect diagnosis need to be incorporated in a model. In **Chapter 3** several existing models were combined to translate and extrapolate the accuracy data into long term health outcomes (lifetime cost-effectiveness) incorporating the whole range from diagnostics to clinical pathway to complications and radiation in the model which can be seen as a challenge. Needless to say, the optimal combination of models was a challenge in and of itself.

UNSOLVED CHALLENGES ENCOUNTERED IN THE CASE STUDIES

Other challenges that were encountered in the case studies estimating the cost-effectiveness of a diagnostic test were multiple testing and the gold standard assumption. In **Chapter 2,** we assumed that the hypothetical test was performed only once at baseline and that it could predict events for the coming ten years. However, it is possible that a test would be repeated more often. Incorporating multiple testing means that the posterior probability depends on the accuracy of the test and the prior probability (previous test result and the prevalence). We were unable to include a multiple testing scenario but we would recommend collecting data on the test results taking into account the dependency between test results, as performed in the CEMARC trial[59]. Furthermore, the optimal timing of the test should be determined; i.e. how often should the test be performed in order to have a good predictive value and acceptable cost-effectiveness.

In **Chapter 3,** it was assumed that ICA was the 'gold standard' when assessing the diagnostic accuracy of NGCCT. However pathological research[248-251] has shown that ICA underestimates the extent and severity of stenosis, resulting in false-negative results and an imperfect sensitivity. Consequently, when a study shows that NGCCT leads to more positive test outcomes than ICA, it would imply that some of these patients have a false positive test (NGCCT positive & ICA negative) which would lead to a lower estimate of the specificity of NGCCT [proportion true negatives (both NGCCT and ICA negative) of all patients with a negative ICA outcome]. To overcome this challenge we would recommend: 1) to perform sensitivity analyses varying accuracy estimates to estimate the impact on the cost-effectiveness, 2) to collect new data on NGCCT using (pathological) research, or 3) to adjust for the gold standard challenge using correlation between the test results.

Besides determining which patient should receive statin therapy (**Chapter 2**) a test potentially could also have an additional effect (e.g. through life style modification) as a result of patients being aware of having a high risk. We were unable to incorporate this additional effect in the model and would recommend in further research that a literature-based model should use a multiplier effect to incorporate the two separate effects of the test into the model. However, the ideal way to deal with the multiple intervention effects challenge is to collect new data focussing on both effects of the test and if necessary to incorporate the additional effects in the analyses.

Multiple indications is a challenge that may only exist in non-pharmaceutical interventions. The cost-effectiveness of pharmaceuticals for different indications can easily be obtained since these interventions are divisible. However, pharmaceuticals are also often used for an off-label indication which should also be evaluated in a cost-effectiveness analysis. In **Chapter 2,** we had a specific decision problem and therefore did not incorporate the cost-effectiveness of NGCCT for other indications. However, such a CT scanner will be used for many other indications and thus a weighted average of its use in multiple applications can be used to estimate the overall value of

both costs and effects in order to decide whether or not to purchase an intervention. In order to estimate a weighted average of its use for all applicants we need to know the relative frequency of each application. Thereafter, the relative frequencies should be combined with the results of the separately performed cost-effectiveness analyses of every application. However, this solution is only possible when the comparators are identical for every indication.
Most (literature-based) models do not incorporate patient heterogeneity. For example, in many models one utility estimate is used for patients without events and several (dis-)utility estimates when events have occurred. As we can see in **Chapter 5** it seems that HRQoL is associated with many clinical characteristics and thus it may be too simple to use one generic utility for all patients assuming a homogenous cohort of patients. Especially, when these characteristics are also associated with the occurrence of clinical events. Consequently, to incorporate all individual differences that may lead to differences in incremental costs and effects there are three options: 1) individual patient level modelling, 2) using aggregate/cohort models subdividing Markov states in separate states to account for all characteristics that are considered important, and 3) performing subgroup analyses. If individual patient data is available, individual patient modelling can be considered as the most sophisticated method.

Determining a structure that adequately includes all significant and clinically relevant events for each individual patient is often challenging. As we could see in **Chapter 6,** where we explored the added value of performing meta-regression analyses, model-based economic evaluations varied considerably in the modelling methods used (e.g. assumptions concerning restenosis, thrombosis or waiting time). In our studies in **Chapters 2, 3 and 7** we also made assumptions to simplify the model. For example, we did not include waiting time in the model but made assumptions concerning the timing of the conversions. Furthermore, we have shown in **Chapter 4** that treatment variation not only exists across countries but also between hospitals; this variation may have an important impact on the structure of the model and may lead to the need to create multiple models. Consequently, the cost-effectiveness of an intervention may differ between studies due to structural uncertainty, since individual studies may have used different assumptions. In **Chapter 9** we have recommended some ways to incorporate structural uncertainty. To improve the comparability of the studies but also to improve the structures of models (i.e. good representation of current disease and treatment pathway), it would be useful if modelling methods (e.g. structural assumptions or time horizon) are standardized for specific decision problems[210] based on expert opinion, clinical guidelines and clinical studies. In addition, researchers should provide sufficient documentation of the methods, including structural assumptions, that were used to estimate the cost-effectiveness of an intervention. This would enable decision makers to determine if the results are transferable or applicable to their own setting (e.g. clinical practice, time horizon, perspective, discount rates, costs).

Lack of data is a challenge that will continue to be present in every economic evaluation, in any form whatsoever (Figure 10.1). In **Chapter 8**, when estimating the cost-effectiveness of fEVAR/

bEVAR, it was decided that it was really too early to populate the model and to perform the analyses since no clinically relevant data was available. The timing of this challenge is often present in non-pharmaceuticals; interventions are used in clinical practice but no comparative data is available to perform a formal assessment. Manufactures of devices do not always have to show effectiveness using RCT data to receive market access approval[233].

OTHER CHALLENGES

In **Chapter 9** we identified and analysed the challenges that currently exist in the field of CVD, based on expert opinion. Some of the reported challenges in this chapter are specific for CVD, but most challenges are present in all types of diseases. Modelling guidelines do not provide sufficient assistance in resolving all challenges but it is probably unrealistic to expect this. Besides identifying where more research is needed, this study provided some directions for researchers about how to deal with modelling challenges when performing CEAs in the area of CVD. Many challenges that were identified in this chapter were recognized in the case studies, these include multiple testing and multiple indications (Table 10.1). Beside the challenges presented in the case studies, we also recognized challenges like compliance and persistence, and process utilities. However, in our case studies we did not have to deal with those challenges and thus only recommendations based on other studies can be provided. In chapter 9, we provided suggestions to deal with those challenges.

TIMING OF CHALLENGES

Estimating the cost-effectiveness of an intervention that is accurate, recent and generalizable to the whole population always implies overcoming challenges. The frequency and the importance of the challenge are often dependent on the timing of the CEA and the stage of research that is performed at the time of the study (Figure 10.1). Three stages of research were defined; 1) research before clinical use, 2) research before market access and 3) research after market access, which are dependent on the medical product development process and the clinical use of the intervention. Depending on the type of research that has been performed and the objective of the study we can distinguish two types of health technology assessment (HTA): (very) early HTA and classic HTA. (Very) early HTA estimates the potential cost-effectiveness of a technology for manufacturers and investors of the technology using evidence from early bench and animal testing, early clinical experience, previous generations of the technology[252] and assumptions (research before clinical use). Classic HTA estimates the current cost-effectiveness of a technology for regulators, payers and patients using clinical studies performed with the technology[252] (research before and after market access).

Many challenges are present across all stages of research. Therefore, when challenges are present in more than one stage of research, we specified what exactly can be a challenge for HTA based on research stage and clinical uptake. For example, the challenge regarding a learning curve is present when HTA is based on research that is performed before or after market access. Before market access, the experience with the technology by clinical pioneers is still increasing. Therefore, estimating the cost-effectiveness of the technology at that specific time would imply that it will not reflect the real cost-effectiveness since it is likely that complications are more frequent than when a physician have reached the plateau of the learning curve. This phenomenon was also seen in the trials evaluating EVAR; physicians were still improving and devices were improved and consequently reinterventions were reduced in the years after the trials. Consequently, the cost-effectiveness of EVAR versus OSR based on the trials was less favourable than it currently is. After market access, the technology will diffused to peripheral hospitals and physicians there will need to learn the procedure. Subsequently, the initial frequency of complications may be relatively high but also decrease over time. Ideally, to obtain a valid and accurate cost-effectiveness estimate, the technology should be fully adopted by the physicians and the quality of the procedure should met an acceptable standard. However, evaluating the cost-effectiveness of a fully adopted intervention might also be considered too late since it takes years to reach the plateau of the learning curve[253], especially in procedures like fEVAR/bEVAR that are not performed very frequently. Furthermore, newer versions which are easier to use come to the market. However, it could be argued that complications during the learning process should also be incorporated in the assessment since this is part of what actually happens in daily practice. One could examine the cost-effectiveness with the first patients separately from the cost-effectiveness with patients treated later and estimate a weighted average of the cost-effectiveness results. In any case, it is clear that accounting for a learning curve in a cost-effectiveness analysis is a complicated challenge.

FURTHER RESEARCH

Further research is required to deal with the challenges (e.g. multiple testing) that were unsolved in the case studies and the additional challenges (e.g. compliance and persistence) that were identified in chapter 9. In addition, to have a more thorough overview of the challenges that may be encountered in assessing the cost-effectiveness of CVD interventions we would recommend case studies in other cardiovascular disease areas like peripheral vascular disease or congenital heart disease since these diseases are not covered in this thesis. However, the reported challenges in this thesis may also apply to these other types of CVD since the types of treatment that are used in those types are fairly comparable to those discussed in this thesis. This thesis provided a first attempt to provide an overview of the timing of the challenges which could be improved if more case studies are performed.

Table 10.1 | Overview of challenges identified in chapters

Challenges	Solved case	Unsolved case	Other
Data requirement challenges			
1 Lack of relevant data	2,7	8	
1a Treatment effectiveness	7	8	
1b Prevalence/prior			9
1c Accuracy data	2	3	
1d Compliance & persistence			9
1e Quality of life		8	
1f Resource use	7	8	
1g Unit costs	2,7	8	
1l Indirect costs			9
1h Missing values			9
1i Parameter distributions		8	
1j Adverse events		8	
1k Subpopulation data			9
2 Combining sources	3		

Challenges	Solved case	Unsolved case	Other
Modelling challenges			
1 Structure		4,6	
1a Comparators			9
1b Disease pathway		2,3,4,6,7	
1c Time horizon			9
2 Heterogeneity		5	
3 History			9
4 Extrapolating short/intermediate results	3		
5 Competing risks			9
6 Multiple testing		2	
7 Multiple interventions effects		2	
8 Learning curve	7		
9 Wait time (e.g. capacity constraints)		7	
10 Multiple indications		3	
11 Lead time			9
12 Reusability			9
13 Process utilities			9
14 Scenario analyses			9

GENERAL CONCLUSIONS

Based on the studies presented in this thesis we can conclude that assessing the cost-effectiveness of cardiovascular disease interventions always requires overcoming many challenges. Some can be 'solved' by gathering additional data and using sensitivity analyses while others require more sophisticated methods such as individual patients simulations. In some cases, it may not be possible to obtain a valid estimate of the cost-effectiveness of an intervention. Many challenges arise as the result of lack of data and thus it is necessary to obtain reliable and sufficient data to assess a valid, accurate and relevant cost-effectiveness estimate for a CVD intervention.

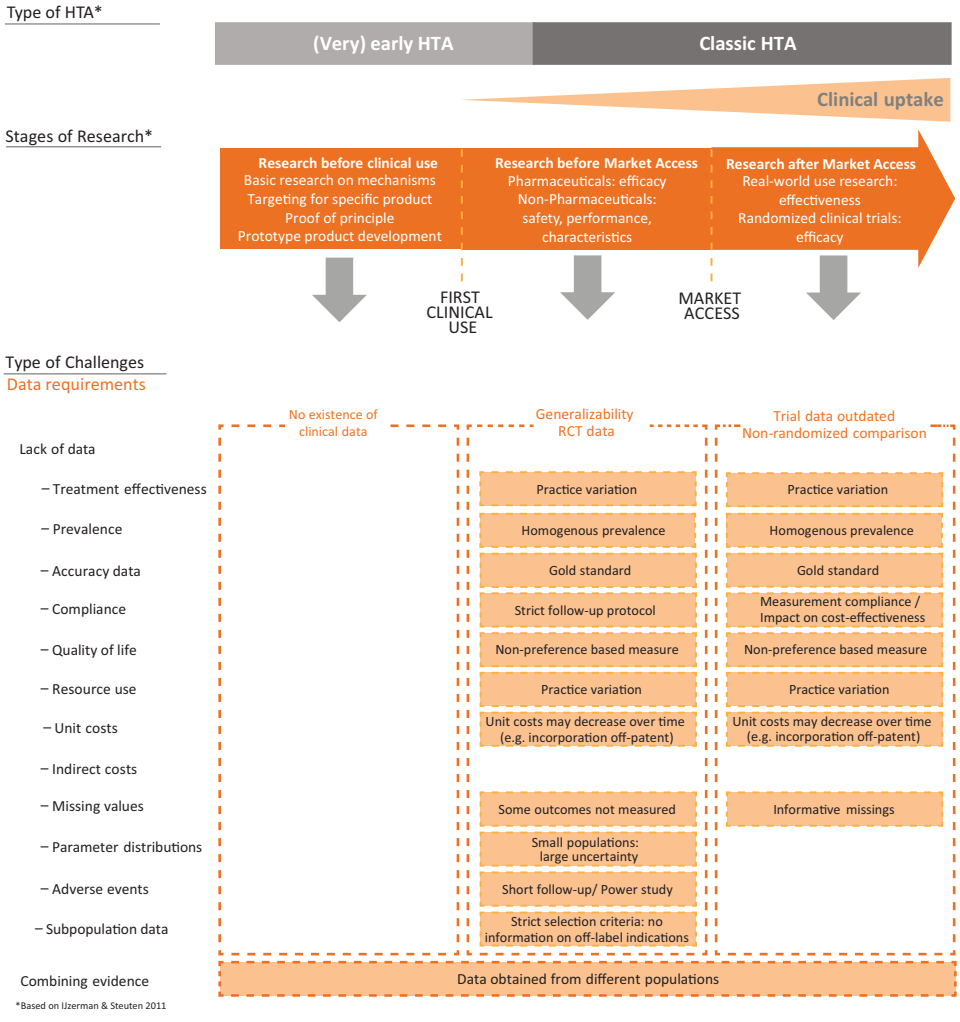

Figure 10.1 | Timing of challenges

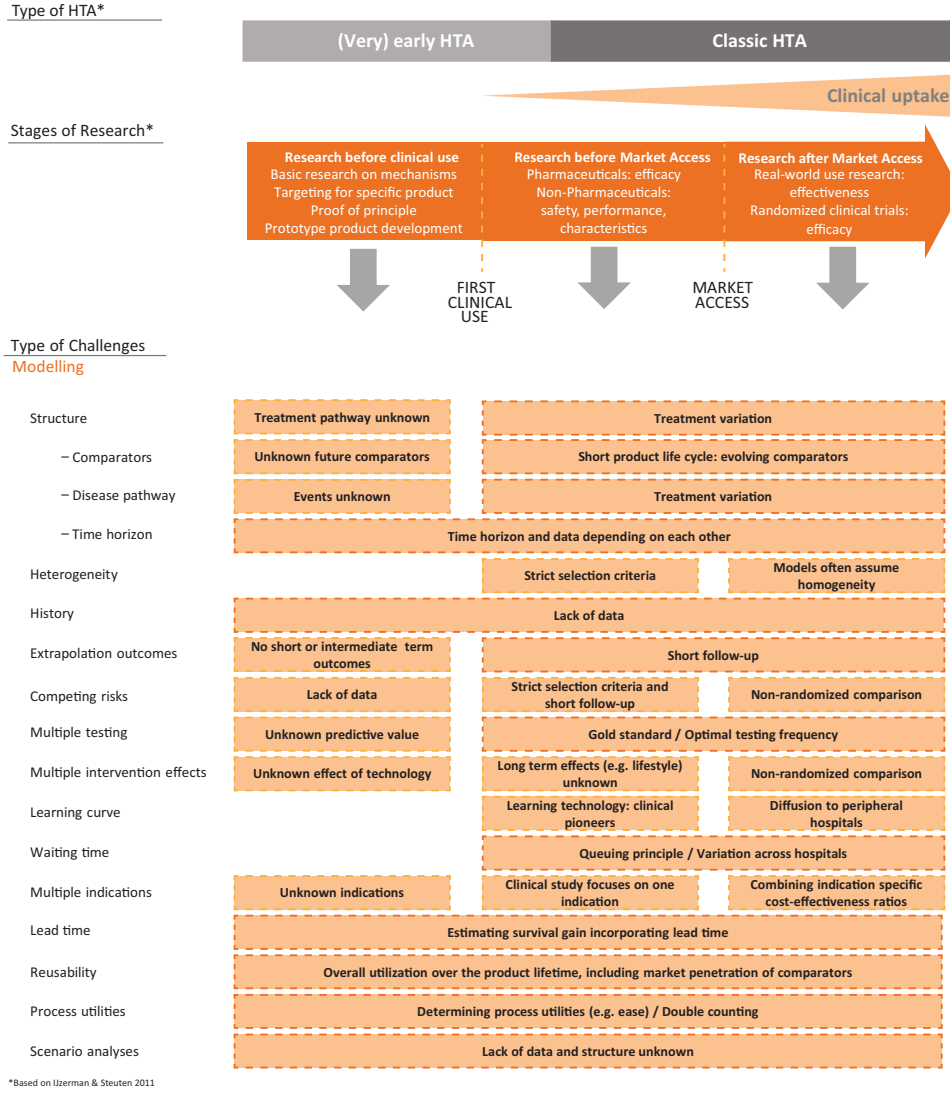

Figure 10.1 | *(Continued)*

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Summary

INTRODUCTION

Since healthcare expenditures are expected to rise in the future due to aging and the development of new medical technologies, it is necessary to spend the healthcare budget wisely. Cost-effectiveness analyses (CEA) can feed into making choices in allocating limited health care resources. Cardiovascular diseases (CVD) accounts for 9.2% of the total health care expenditure in the Netherlands. In this area many non-pharmaceutical technologies (e.g. stents, prostheses or diagnostic tests) are used to diagnose and treat patients with CVD. In the previous years, many new or improved non-pharmaceutical technologies came to the market and therefore it is important to estimate if these interventions are cost-effective compared to existing interventions. However, it is often challenging to accurately estimate the cost-effectiveness of these interventions due to a number of reasons.

In this thesis, the aim was to assess the cost-effectiveness of various technologies in CVD and to identify and deal with challenges in the cost-effectiveness analysis methods. Several case studies were performed to identify the challenges and a review was performed to provide an overview of the challenges that arise in modelling the cost-effectiveness of cardiovascular interventions. The case studies focussed on the cost-effectiveness of diagnostic tests for primary and secondary prevention of CVD and coronary artery disease (CAD) and treatment strategies for CAD and aortic aneurysms. In addition, analyses of treatment variation and health related quality of life of patients diagnosed with CAD are performed.

CASE STUDIES

In **Chapter 2** we estimated the potential cost-effectiveness of a biomarker test that could be used to decide which individuals with an intermediate CVD risk would benefit from statin treatment. Prognosis of different age- and gender-specific cohorts was simulated with a Markov model to estimate the potential costs and quality-adjusted life-years for four strategies: treat all with statins, treat none with statins, treat according to the European guidelines, or use a test to select individuals for statin treatment. We concluded that a perfect hypothetical test would dominate the other strategies if the test did not cost more than €237, consequently a less-than-perfect test would have to cost less than €237.

New generation dual-source coronary CT (NGCCT) scanners were evaluated in **Chapter 3** for patients with known or suspected CAD who are difficult to image. The cost-effectiveness was assessed for three strategies: use of invasive coronary angiography (ICA) only, ii) use of NGCCT only, and iii) use of a combination of NGCCT and (in the event of positive NGCCT) ICA. Extensive modelling, combining several models, was performed to estimate the cost-effectiveness of NGCCT for both CAD populations, separately. We concluded that the use of NGCCT might be considered as cost-effective in both populations since it is cost-saving compared to ICA and it generates similar health effects.

In **Chapter 4** we explored what factors are associated with variation in stent choice in patients undergoing a percutaneous coronary intervention (PCI), based on a prospective cohort of Dutch patients with unstable or stable CAD treated with bare-metal stents (BMS) or drug-eluting stents (DES). Using multiple logistic regression analyses we showed that besides clinical factors, which may be considered as legitimate reasons for variation, the treating hospital was also associated with type of stent. This association with stent choice could arise because of financial arrangements with stent manufacturers, budget constraints or operators preferences (believers versus non-believers of DES) which may lead to differences in long-term outcomes.

In **Chapter 5** we performed multiple linear regressions to identify variables that are significantly associated with health related quality of life (HRQoL) and short form (SF)-36 component scores in Dutch patients with stable and unstable CAD. We observed significant associations with gender, systolic blood pressure, body-mass index, previous PCI, NYHA class, previous cerebrovascular accident or transient ischaemic attack, peripheral vascular disease, pack-years (tobacco) and pulmonary disease in the stable CAD group. Unstable CAD patients had higher average physical component score, mental component score and SF-36 dimension scores than stable CAD patients. The mental health dimension was the least affected dimension of the SF-36 but CAD had a negative impact on the physical dimensions. Knowledge of these associations can help to identify ways to improve care (e.g. increase physical activity) and thereby improve HRQoL.

In **Chapter 6** we presented a case study, a systematic review on the cost-effectiveness of DES versus BMS using meta-regression analyses exploring the usefulness of such methods compared with conventional review methods. The meta-regressions showed associations (e.g. type of lesion) that were expected (based on individual studies), however we also revealed unpredicted associations: e.g. model quality was negatively associated with the number of repeat revascularizations avoided. Consequently, meta-regressions can be of added value, identifying significant associations that could not be identified using conventional review methods or sensitivity analyses of individual studies.

Patients with a large unruptured AAA can be treated electively with endovascular aneurysm repair (EVAR) or open surgical repair (OSR). An existing model estimating the lifetime cost-effectiveness of EVAR for the UK was adopted for the Netherlands in **Chapter 7**. EVAR and OSR can be considered equally effective and in addition EVAR was cost-saving compared with OSR. Thus EVAR can be considered as a cost-effective solution for patients with AAA, however this is highly dependent on the price of an EVAR device and the degree to which EVAR reduces hospital days, complications and 30-day mortality.

Besides estimating the cost-effectiveness of EVAR versus OSR we have described how the cost-effectiveness of fenestrated and branched EVAR (fEVAR/bEVAR) should be estimated in **Chapter 8** using the NICE guidelines on technology appraisal methods. We showed that the framing phase and the first two steps of the assessment phase could be performed. However, we were unable to populate the model and estimate the cost-effectiveness of fEVAR/bEVAR since no evidence on efficacy and costs were available. It therefore remains uncertain whether the extra cost of fEVAR/bEVAR is justified by the advantages for patients.

OVERVIEW CHALLENGES

In **Chapter 9** we identified and analysed the challenges that currently exist in the field of CVD, using review methods. Lack of effectiveness data and quality-of-life data, determining a model structure, and extrapolating short- or intermediate-term results, are very frequently reported or implied challenges. Modelling guidelines do not provide sufficient assistance in resolving all challenges but it is probably unrealistic to expect this. Besides identifying where more research is needed, this study provided some directions for researchers about how to deal with modelling challenges when performing CEAs in the area of CVD.

DISCUSSION

Chapter 10 discusses the main findings of the case studies and describes the challenges that were encountered in the case studies. Beside the challenges that were (un)solved in the case studies we described also the challenges that were identified in the review performed in chapter 9 but were not encountered in the case studies. Furthermore, suggestions to solve the challenges are provided. Moreover, we linked the timing of the study (early HTA versus classical HTA) and the type of clinical research with the type of challenges that may encounter during a study evaluating the cost-effectiveness of a cardiovascular intervention.

Based on this thesis we could conclude that assessing the cost-effectiveness of cardiovascular disease interventions requires always overcoming many challenges. Some can be 'solved' using gathering additional data, using sensitivity analyses others require more sophisticated methods such as individual patients simulations. In some cases, it is even not possible to estimate the cost-effectiveness of an intervention validly, it was too early. Many challenges are the result of lack of data and thus it is necessary to obtain reliable and sufficient data to assess a valid, accurate and relevant cost-effectiveness estimate for a CVD intervention.

Samenvatting

Een verantwoorde verdeling van het gezondheidszorgbudget is belangrijk gegeven de verwachte verdere stijging in gezondheidszorguitgaven vanwege de vergrijzing van de samenleving en de ontwikkeling van nieuwe medische technologieën. Kosteneffectiviteitsanalyses in combinatie met budgetimpact analyses kunnen helpen in het bepalen van de efficiëntie van een technologie en hoe het gezondheidszorgbudget zinnig verdeeld kan worden. In Nederland wordt 9,2% van de totale uitgaven aan de gezondheidszorg besteed aan hart- en vaatziekten (HVZ). Bij HVZ worden veel niet-farmacologische technologieën [bijv. stents, prothesen of (beeldvormende) diagnostiek] gebruikt voor de diagnostisering en behandeling van patiënten met HVZ. Het is belangrijk om de kosteneffectiviteit van deze interventies in kaart te brengen, met name omdat er in de afgelopen jaren veel nieuwe of verbeterde niet-farmacologische interventies op de markt zijn verschenen. Om verschillende redenen is het een uitdaging om een valide schatting te maken van de kosteneffectiviteit van dit type interventies.

Het doel van dit proefschrift was het berekenen van de kosteneffectiviteit van verschillende cardiovasculaire interventies en het in kaart brengen van de daarmee gepaard gaande onderzoeks-methodologische uitdagingen. Verschillende casestudies zijn uitgevoerd om deze uitdagingen te identificeren en een review is uitgevoerd om een overzicht te geven van de uitdagingen die ontstaan wanneer men de kosteneffectiviteit van een cardiovasculaire interventie modelleert. De casestudies richtten zich op de kosteneffectiviteit van diagnostische interventies voor primaire en secundaire preventie van HVZ maar ook op de kosteneffectiviteit van behandelstrategieën voor coronaire hartziekte en aneurysmata van de aorta. Verder is behandelvariatie en kwaliteit van leven van patiënten met coronaire hartziekte onderzocht.

CASESTUDIES

In **hoofdstuk 2** is de potentiele kosteneffectiviteit berekend van een hypothetische biomarker test die gebruikt kan worden om te bepalen of individuen met een intermediair HVZ risico behandeld zouden moeten worden met statines. Ziektebeloop van verschillende leeftijd en geslacht specifieke cohorten is gemodelleerd met behulp van een Markov model. De kosteneffectiviteit is berekend voor vier verschillende behandelstrategieën: 1) iedereen behandelen met statines, 2) niemand behandelen met statines, 3) behandelen volgens de huidige Europese richtlijn of 4) het gebruik van een test om te bepalen welke patiënten statines zouden moeten krijgen. Uit deze studie bleek dat een perfecte hypothetische test de andere strategieën zou domineren wanneer de test niet meer dan €237 kost.

In **hoofdstuk 3** is de kosteneffectiviteit berekend van de nieuwe generatie dual-source CT-scanners (NGCCT) voor patiënten met coronaire hartziekten of die verdacht worden van coronaire hartziekten waarbij de oudere generatie CT-scanners niet afdoende zijn (bijv. obesitas, aritmie). De kosteneffectiviteit van drie diagnostische strategieën is bepaald: 1) invasieve coronaire angiografie (ICA), 2) NGCCT of 3) een combinatie van NGCCT en ICA (wanneer NGCCT positief is). Verschillende beslismodellen zijn gecombineerd om de kosteneffectiviteit van NGCCT te berekenen waarbij in ogenschouw werd genomen: korte termijn accuraatheid, gevolgen van stralingsbelasting en lange termijn kosten en gezondheidsuitkomsten (overleving, kwaliteit van leven, klinische events). Uit deze studie bleek dat de NGCCT kosteneffectief kan zijn voor patienten met coronaire hartziekten en voor patienten die verdacht worden van coronaire hartziekten, omdat NGCCT leidt tot kostenbesparingen en resulteert in gelijkwaardige effectiviteit ten opzichte van ICA.

In **hoofdstuk 4** is onderzocht welke factoren geassocieerd zijn met de stent keuze voor patiënten die een percutane coronaire interventie (PCI) ondergaan. Deze studie is gebaseerd op een cohort van Nederlandse patiënten (Circulating Cells studie) met instabiele of stabiele coronaire hartziekten die behandeld worden met een bare-metal stent (BMS) of een drug-eluting stent (DES). Op basis van verschillende logistische regressies kunnen we concluderen dat naast klinische aspecten ook het behandelend ziekenhuis geassocieerd was met de stent keuze. Deze associatie kan het gevolg zijn van prijsafspraken met stent fabrikanten, budget afspraken of voorkeuren van artsen. De variatie in stent keuze kan leiden tot verschillen in langer termijn klinische uitkomsten zoals trombose of restenose.

Hoofdstuk 5 is net als hoofdstuk 4 gebaseerd op de Circulating Cells cohort studie. In dit hoofdstuk is met behulp van verschillende lineaire regressies, getracht te onderzoeken welke factoren significant geassocieerd zijn met gezondheidsgerelateerde kwaliteit van leven en SF-36 component scores bij patiënten met stabiele of instabiele coronaire hartziekten. Significante associaties met kwaliteit van leven zijn gevonden met geslacht, systolische bloeddruk, body mass index (BMI), eerdere PCI, New York Heart Association (NYHA) klasse, eerdere transient ischemic attack (TIA) of beroerte, aanwezigheid van perifeer vaatlijden, aantal pakjaren (roken) en aanwezigheid van longaandoeningen in de stabiele angina groep. Gemiddeld hebben de instabiele patiënten een hogere fysieke component score, mentale component score en SF36 domein scores dan de stabiele angina patiënten. De mentale component score is het minste aangedaan door coronaire hartziekte, de fysieke component score is het meeste negatief beïnvloed door coronaire hartziekte. Kennis van deze associaties kan helpen om manieren te vinden om de zorg voor patiënten met coronaire hartziekten te verbeteren zoals het aanmoedigen van fysieke inspanning.

De resultaten van een systematische review van de kosteneffectiviteit van drug-eluting stents versus bare-metal stents zijn gepresenteerd in **hoofdstuk 6**. De bruikbaarheid van meta-regressie analyses bovenop de conventionele systematische review methode is bekeken in deze casestudie. Naast de verwachte associaties zijn met behulp van de meta-regressie analyses ook associaties gevonden die met een conventionele systematische review niet naar voren zouden komen: de kwaliteit van de studies is negatief geassocieerd met het aantal vermeden opnieuw uitgevoerde PCIs. Deze casestudie laat zien dat meta-regressies waardevol kunnen zijn in het verklaren van verschillen in uitkomsten tussen kosteneffectiviteitsanalyses ten opzichte van conventionele review methoden of onzekerheidsanalyses van individuele studies.

Patiënten met een groot ongeruptureerd abdominaal aorta aneurysma (AAA) kunnen electief behandeld worden met een endovasculaire (EVAR) of open (OSR) behandeling van het aneurysma. Een bestaand model dat de levenslange kosteneffectiviteit van EVAR versus OSR heeft berekend voor Groot-Britannië is aangepast naar de Nederlandse setting. **Hoofdstuk 7** laat zien dat de effectiviteit van EVAR en OSR gelijkwaardig is aan elkaar maar dat EVAR leidt tot een kostenbesparing. Hieruit kan geconcludeerd worden dat EVAR een kosteneffectieve oplossing is voor patiënten met AAA. De mate van kosteneffectiviteit is sterk afhankelijk van de kosten van het EVAR device en de reductie in opnamedagen, complicaties en 30-dagen mortaliteit als gevolg van EVAR.

Naast het schatten van de kosteneffectiviteit van EVAR versus OSR is in **hoofdstuk 8** beschreven hoe de kosteneffectiviteit van gefenestreerde (fEVAR) en branched (bEVAR) EVAR berekend moet worden aan de hand van de NICE richtlijnen. Deze studie laat zien dat het mogelijk was om de framing fase en de eerste twee stappen van de assessment fase uit te voeren. Het was dus niet mogelijk om voldoende betrouwbare data te vinden om de kosteneffectiviteit van fEVAR/bEVAR te berekenen. Het is onduidelijk of de extra kosten van een fEVAR/bEVAR procedure (met name de prothese) opwegen tegen de klinische voordelen voor de patiënt.

OVERZICHT UITDAGINGEN

In **hoofdstuk 9** hebben is met behulp van een review geïdentificeerd en geanalyseerd welke uitdagingen er op dit moment zijn op het gebied van het modelleren van cardiovasculaire interventies. De meest gerapporteerde en geïmpliceerde uitdagingen zijn: gebrek aan data over effectiviteit en kwaliteit van leven, het bepalen van de meest geschikte model structuur en het extrapoleren van korte termijn en intermediaire uitkomsten. Modelleringsrichtlijnen zijn niet in staat om voor alle uitdagingen aanbevelingen te doen. Naast het identificeren van de uitdagingen waar nog onderzoek naar gedaan moet worden, biedt deze studie handvatten voor onderzoekers om uitdagingen op het gebied van cardiovasculaire interventies op te lossen.

DISCUSSIE

In **hoofdstuk 10** worden de conclusies van de gepresenteerde casestudies bediscussieerd en worden de uitdagingen van deze casestudies beschreven. Naast deze uitdagingen worden ook de uitdagingen die uit de review uit hoofdstuk 9 naar voren kwamen aangehaald. Bovendien worden ook nog suggesties gedaan om een aantal van deze uitdagingen op te lossen. Verder hebben we de timing van de studie (vroege HTA versus klassieke HTA) en het type klinische onderzoek gelinkt aan het type uitdaging die voor kan komen tijdens het berekenen van de kosteneffectiviteit van een cardiovasculaire interventie.

Op basis van dit proefschrift kunnen we concluderen dat het berekenen van de kosten-effectiviteit van een cardiovasculaire interventie altijd gepaard gaat met het overwinnen van onderzoeksmethodologische uitdagingen. Sommige van deze uitdagingen kunnen opgelost worden door meer data te verzamelen of onzekerheid analyses uit te voeren terwijl andere uitdagingen meer geavanceerde methoden vereisen zoals individuele patiëntsimulatietechnieken. In sommige gevallen is het zelfs onmogelijk om een valide en accurate schatting van de kosteneffectiviteit van een interventie te maken omdat het te vroeg in het proces was. De meeste uitdagingen zijn het gevolg van niet beschikbare data en daarom is het belangrijk om voldoende betrouwbare data te verzamelen. Met deze data kan een valide, accurate en relevante schatting gemaakt worden van de kosteneffectiviteit van een cardiovasculaire interventie.

List of publications

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PhD portfolio

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2010	Presentation course – Nederlandse organisatie voor Wetenschappelijk Onderzoek
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2010–2012	Research Master Clinical Epidemiology – Erasmus Medical Center / NIHES
2013	Mentor training, studeercoach

Teaching

2010	Introductie week, practicum – bachelor program Health sciences, institute of Health Policy and Management, Erasmus University Rotterdam
2010–2015	Supervision for 7 thesis students, bachelor and master program – institute of Health Policy and Management, Erasmus University Rotterdam
2010–2015	Co-evaluator for 7 thesis students, bachelor and master program – institute of Health Policy and Management, Erasmus University Rotterdam
2011	Minor Health technologies and their valuation, group assignments, working groups, coordination, preparation exam – bachelor program Health sciences, institute of Health Policy and Management, Erasmus University Rotterdam
2011–2012	International value coalition, practicum
2012	Minor De toekomst van de zorg: medische technologie, group assignments, lecture, working groups, coordination, preparation exam – bachelor program Health sciences, institute of Health Policy and Management, Erasmus University Rotterdam
2012	Sociaal medische wetenschappen, working groups – bachelor program Health sciences, institute of Health Policy and Management, Erasmus University Rotterdam
2012	International Health Policy and Economics: Diplome course cost-effectiveness modelling methods, practicum – institute of Health Policy and Management, Erasmus University Rotterdam

2012–2013	Health Economics, practicum – NIHES
2012–2014	Health Technology Assessment, practicum – Master program Health Economics, Policy and Law, institute of Health Policy and Management, Erasmus University Rotterdam
2012–2014	Praktijkstage, working groups, essays – bachelor program Health sciences, institute of Health Policy and Management, Erasmus University Rotterdam
2013–2015	Tutor, working groups – bachelor program Health sciences, institute of Health Policy and Management, Erasmus University Rotterdam
2013–2015	Stage het primaire proces, tutor – bachelor program Health sciences, institute of Health Policy and Management, Erasmus University Rotterdam
2014	Participating in HTA research, working groups – Master program Health Economics, Policy and Law, institute of Health Policy and Management, Erasmus University Rotterdam

Conferences

Podium presentations

2013	Challenges in modelling the cost effectiveness of interventions in cardiovascular disease – ISPOR, Dublin, Ireland
2013	A systematic review was performed to gain insight into whether modelling methods influence the estimated cost-effectiveness – LOLA HESG, Nunspeet, The Netherlands
2012	Is it worth spending any money to develop a biomarker test to optimize statin treatment for individuals with an intermediate cardiovascular risk? – ISPOR, Berlin, Germany
2010	Medical Technology Assessment – Annual meeting Circulating Cells, Rotterdam

Poster presentation

2014	Cost-effectiveness of disease management programs for cardiovascular risk and COPD in the Netherlands – ISPOR, Amsterdam, The Netherlands
2014	Cost analysis of two aftercare strategies in chronic continuous intrathecal baclofen therapy in patients with intractable spasticity – ISPOR, Amsterdam, The Netherlands
2013	Decision analytic models used in estimating the cost-effectiveness of drug-eluting stents versus bare-metal stents: a systematic review – ISPOR, Dublin, Ireland
2013	Economic Evaluation of Mandibular Advancement Device to Treat Obstructive Sleep Apnea – ISPOR, Dublin, Ireland
2012	Is it worth spending any money to develop a biomarker test to optimize statin treatment for individuals with an intermediate cardiovascular risk? – Annual meeting CTMM, Utrecht

2011 Using five existing models to comprehensively model the cost-effectiveness of a high definition CT scanner in a coronary artery disease population: a nice diagnostic guidance project – ISPOR, Madrid, Spain

2011 Decision analytic models used in estimating the cost-effectiveness of drug-eluting stents versus bare-metal stents – ISPOR, Madrid, Spain

2010 Potential cost-effectiveness of a biomarker test to reclassify patients with an intermediate risk based on the Framingham Risk Score into a lower or higher category to optimize statin therapy – Annual meeting CTMM, Utrecht

2010 Potential cost-effectiveness of a biomarker test to reclassify patients with an intermediate risk based on the Framingham risk score into a lower or higher category to optimize statin therapy – ISPOR, Prague, Czech Republic

2010 Potential cost-effectiveness of a biomarker test to stratify patients indicated for a coronary stent – ISPOR, Prague, Czech Republic

Moderator

2014 Diagnostic research – ISPOR, Amsterdam, The Netherlands

Presentation at other meetings

2014 Cost-effectiveness analyses of diagnostic tests, Honours class Biomedical Technology – LUMC

2012 Cost-effectiveness analysis of a new generation coronary CT scanner: a NICE diagnostic assessment rapport – institute of Health Policy and Management

2012 Cost-effectiveness analyses in cardiology: one link between treatment choices, patient outcomes and policymaking – REMOTE CIED, Tilburg University

Reviewing

2015 BMC cardiovascular disorders

2013–2014 Value in Health

Awards

2012 Best new investigator research presentation podium awards, ISPOR, Berlin, Germany

2011 Nomination, Best new investigator research presentation poster awards, ISPOR, Madrid Spain

2010 Best new investigator research presentation poster awards, ISPOR, Prague, Czech Republic

About the author

Laura Theodora Burgers was born on June 25 1987 in Moordrecht, the Netherlands. In 2005 she graduated from high school at Sint-Antonius College in Gouda and started with the bachelor Health Sciences at the Erasmus University in Rotterdam (2005–2008). In 2010, she obtained her Master's degree in Health Economics Policy and Law, specialization Health Economics at the Erasmus University Rotterdam. In addition, she has successfully followed the Research Master Clinical Epidemiology at the Netherlands Institute for Health Sciences / Erasmus University Rotterdam (2010–2012). Since 2010 she is a PhD candidate at the Institute of Health Policy and Management (iBMG), Erasmus University Rotterdam under the supervision of Prof.Dr. Hans Severens and Dr. Ken Redekop. Her research mainly focused on the cost-effectiveness of medical devices and diagnostic tests in the prevention and treatment of cardiovascular diseases based on modelling studies.

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Since healthcare expenditures are expected to rise in the future due to aging and the development of new medical technologies, it is necessary to spend the healthcare budget wisely. Cost-effectiveness analyses can feed into making choices in allocating limited health care resources. Cardiovascular diseases account for a large proportion of the total health care expenditure in the Netherlands. In this area many non-pharmaceutical technologies (e.g. stents, prostheses or diagnostic tests) are used to diagnose and treat patients with cardiovascular diseases. In the previous years, many new or improved non-pharmaceutical technologies came to the market and therefore it is important to estimate if these interventions are cost-effective compared to existing interventions. However, it is often challenging to accurately estimate the cost-effectiveness of these interventions due to a number of reasons. In this dissertation, the aim was to assess the cost-effectiveness of various technologies in cardiovascular diseases and to identify and deal with challenges in the cost-effectiveness analysis methods.