Linköping University Medical Dissertations No. 1011

Cost-Effectiveness and Value of Further Research of Treatment Strategies for Cardiovascular Disease

Martin Henriksson

Center for Medical Technology Assessment
Department of Medicine and Health Sciences
Linköping University, Sweden

Linköping 2007

Printed in Sweden by LiU-Tryck, Linköping, Sweden, 2007

ISBN 978-91-85831-20-3
ISSN 0345-0082

To Elin, Karl and Frans

‘It is better to be roughly right than precisely wrong’

John Maynard Keynes

CONTENTS

ABSTRACT

Economic evaluations provide a tool to estimate costs and health consequences of competing medical technologies, ultimately to aid decision makers when deciding which medical technologies should be funded from available resources. Such decisions inevitably need to be taken under uncertainty and it is not clear how to approach them in health care decision-making. Recent work in economic evaluation has proposed an analytic framework where two related, but conceptually different decisions need to be considered: (1) should a medical technology be adopted given existing evidence; and (2) whether more evidence should be acquired to support the adoption decision in the future. The proposed analytic framework requires a decision-analytic model appropriately representing the clinical decision problem under consideration, a probabilistic analysis of this model in order to determine cost-effectiveness and characterise current decision uncertainty, and estimating the value of additional information from research to reduce decision uncertainty. The main aim of this thesis is to apply the analytic framework on three case studies concerning treatment strategies for cardiovascular disease in order to establish whether the treatment strategies should be adopted given current available information and if more information should be acquired to support the adoption decisions in the future. The implications for policy and methodology of utilising the analytic framework employed in the case studies are also discussed in this thesis.

The results of the case studies show that a screening programme for abdominal aortic aneurysm in 65-year-old men is likely to be cost-effective in a Swedish setting and there appears to be little value in performing further research regarding this decision problem; an early interventional strategy in non-ST-elevation acute coronary syndrome is cost-effective for patients at intermediate to high risk of further cardiac events in a UK setting; endarterectomy in patients with an asymptomatic carotid artery stenosis is cost-effective for men around 73 years of age or younger in a Swedish setting and conducting further research regarding this decision problem is potentially worthwhile.

Comparing the results of the present analyses with current clinical practice shows a need for changing clinical practice in Sweden regarding screening for abdominal aortic aneurysm and endarterectomy in patients with asymptomatic carotid artery stenosis. Furthermore, employing the analytic framework applied in the case studies can improve treatment guidelines and recommendations for further research. In particular, treatment guidelines ought to consider in which particular subgroups of patients an intervention is cost-effective.

The case studies indicate that it is feasible to apply the analytic framework for economic evaluation of health care. Methodological development can improve the accuracy with which cost-effectiveness and value of information is estimated, but may also lead to comprehensive and complex evaluations. The nature of the decision problem should determine the level of comprehensiveness required for a particular evaluation.

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Henriksson M, Lundgren F. Decision-analytical model with lifetime estimation of costs and health outcomes for one-time screening for abdominal aortic aneurysm in 65-year-old men. *British Journal of Surgery* 2005; 92(8):976-983.

II. Henriksson M, Lundgren F, Carlsson P. Informing the efficient use of health care and research resources – the case of screening for abdominal aortic aneurysm in Sweden. *Health Economics* 2006;15(12):1311-1322.

III. Henriksson M, Epstein D, Palmer S, Sculpher M, Clayton T, Pocock S, Henderson R, Buxton M, Fox K A A. The cost-effectiveness of an early interventional strategy in Non-ST-elevation acute coronary syndrome based on the RITA 3 trial. (Submitted)

IV. Henriksson M, Lundgren F, Carlsson P. Cost-effectiveness of endarterectomy in patients with asymptomatic carotid artery stenosis in Sweden. (Submitted)

V. Henriksson M, Lundgren F, Carlsson P. The value of further research into the cost-effectiveness of endarterectomy in patients with asymptomatic carotid artery stenosis in Sweden. (Submitted)

ABBREVIATIONS

AAA	Abdominal aortic aneurysm
ACST	Asymptomatic Carotid Surgery Trial
BMT	Best medical treatment
CEA	Carotid endarterectomy
CVD	Cardiovascular death
ENBS	Expected net benefit of sampling
EQ-5D	EuroQol-5 dimensions
EVPI	Expected value of perfect information
EVPPI	Expected value of perfect partial information
EVSI	Expected value of sample information
FRISC II	Fast Revascularisation during Instability in Coronary artery disease
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICTUS	Invasive versus Conservative Treatment in Unstable Coronary Syndromes
ICU	Intensive care unit
INB	Incremental net benefit
MI	Myocardial infarction
NB	Net benefit
NHS	National Health Service
NSTE-ACS	Non-ST-elevation acute coronary syndrome
QALY	Quality-adjusted life year
RITA 3	third Randomised Intervention Trial of unstable Angina
SBU	Swedish Council on Technology Assessment in Health Care
SEK	Swedish kronor
SIR	Swedish intensive care registry
SWEDVASC	Swedish Vascular Registry

1. INTRODUCTION

Background

Economic evaluations provide a tool to estimate costs and health consequences of alternative medical technologies in order to establish their cost-effectiveness. If the objective is to maximise health outcomes subject to a resource constraint, the results of economic evaluations aid decision makers when deciding which medical technologies should be funded from available resources [1,2]. These decisions cannot be avoided and inevitably need to be taken despite the fact that the estimated cost-effectiveness is often associated with a high degree of uncertainty. It is not clear how to approach such decisions in health care in order to achieve an efficient allocation of scarce resources.

Principles from decision theory suggest that decisions ought to be based on expected values, i.e., the mean cost-effectiveness, given current available information. The uncertainty associated with decisions based on cost-effectiveness is mainly of importance for the related question of whether to acquire further information to support the decision in the future [3]. However, this has not been the prevailing paradigm when informing decision-making under uncertainty in health care. Rather, based on classical inferential statistics applied in clinical trials, emphasis has been on testing hypotheses about cost-effectiveness to determine whether a new medical technology is significantly more cost-effective than a comparator [4]. The results of this hypothesis testing are then used to guide decisions to adopt a medical technology.

Recent work in economic evaluation of health care has questioned this approach, arguing that it leads to inefficiency in the adoption of medical technologies as rejecting a cost-effective medical technology due to a lack of statistical significance is not consistent with an objective of maximising health outcomes [5]. Instead, an analytic framework has been proposed, arguing that separating the decision to adopt a medical technology and the decision to acquire further information can improve efficiency in the provision of medical

technologies and in research activities [5,6]. The proposed analytic framework requires a decision-analytic model appropriately representing the decision problem under consideration, a probabilistic analysis of the model in order to determine cost-effectiveness and characterise current decision uncertainty, and estimating the value of additional information of research to reduce decision uncertainty.

The principles of this analytic framework for economic evaluation in health care are gaining acceptance and has been taken up by major decision-making bodies outside of Sweden, e.g., the National Institute for Clinical Excellence in the UK [7,8]. However, evaluations fully utilising the proposed analytic framework are still rarely seen in applied work. Hence, it is difficult to assess the extent to which these methods can influence decision-making and clinical practice to date, particularly in Sweden.

In this thesis, the analytic framework is applied to three case studies investigating the cost-effectiveness of management strategies concerned with treatment and prevention of cardiovascular disease: (1) screening for abdominal aortic aneurysm in 65-year-old males; (2) early intervention in patients presenting with non-ST-elevation acute coronary syndrome; and (3) endarterectomy in patients with asymptomatic carotid artery stenosis.

The results of the case studies are intended to provide guidance regarding the adoption of the investigated treatment strategies and whether further information should be acquired to support the adoption decisions in the future. Moreover, the implications for policy and methodology of utilising the analytic framework employed in the case studies are explored. The results of the case studies are compared with current available treatment guidelines, recommendations for further research, and current clinical practice in an attempt to address whether the analytic framework used in the present work has the potential to improve current decision-making and clinical practice. Furthermore, the importance of adequately reflecting uncertainty and heterogeneity in cost-effectiveness has been emphasised in the literature [9], and it is explored if the methods employed in the case studies can be a useful way of achieving this.

Aims

The main aim of this thesis is to apply an analytic framework on three case studies concerning treatment strategies for cardiovascular disease in order to establish whether: (1) the treatment strategies should be adopted given current available information; and (2) whether more information should be acquired to support two of the adoption decisions in the future. Further aims are to investigate the implications for policy and methodology of utilising the analytic framework employed in the case studies.

Outline of thesis

The thesis is structured as follows: chapter 2 provides an overview of the analytic framework applied in the case studies, including a brief introduction to basic concepts of cost-effectiveness analysis and value-of-information analysis; the clinical decision problems investigated in the case studies are introduced in chapter 3; chapter 4 provides the results of the case studies; the results and their implications for policy are discussed in chapter 5; chapter 6 provides a discussion of the implications for methodology of using the analytic framework; and chapter 7 offers some conclusions.

Further details of the case studies are provided in an appendix. Due to the limited space available in journal papers, many relevant details of modelling methods and statistical analyses are reported in technical reports accompanying the papers in this thesis. In the appendix, the interested reader will find details from the technical reports not presented in the papers.

A note on notation

It is useful to clarify some notational points at the outset. The terms medical technology, intervention, treatment strategy and treatment option are used interchangeably and may refer to pharmaceutical treatments, surgical procedures or screening programmes. Although not always synonyms in the literature, economic evaluation and cost-effectiveness analysis will be used interchangeably in this thesis, and refer to establishing and comparing the costs and health outcomes of two or more medical technologies.

Finally, a note on the use of currency in this thesis. The case studies use different currencies, which is somewhat confusing. However, the alternative is to use a common currency in this text, which may confuse the contents of this thesis with that of the papers. Thus, in this uncertain decision between two confusing states of the world, the currencies employed in the case studies are retained in this text. It should be noted that 10 Swedish kronor (SEK) is approximately 1 Euro (€1) or 0.75 pound sterling (£0.75) in August 2007.

2. AN ANALYTIC FRAMEWORK FOR ECONOMIC EVALUATION

This chapter provides an overview of the analytic framework for economic evaluation of medical technologies that is applied in the case studies. As noted in the introduction, economic evaluations are concerned with estimating and comparing costs and health consequences of alternative medical technologies. Such evaluations are needed when deciding which medical technologies should be adopted in a publicly funded health care system, ultimately to ensure that available health care resources are used wisely. Hence, economic evaluations provide a tool to achieve an efficient allocation of scarce health care resources when the objective is to maximise health outcomes subject to a resource constraint [1,2].

There are different views regarding the appropriate definition of health outcomes and what constitutes the relevant resource constraint. The different views are mainly the result of adopting different perspectives for the analyses. Based on welfare economics, some argue that a societal perspective is necessary, implying that all costs and consequences associated with different treatment strategies should be included in the analysis. Others argue that a health care perspective is appropriate, implying that only costs related to health care and a relevant health outcome associated with different treatment strategies should be included in the analysis. The merits of each approach have been discussed at length in the literature [10-12]. In the case studies, the perspective of the analyses is clearly defined and no attempt is made in this thesis to establish which perspective is 'correct'.

Irrespective of the perspective adopted, available resources can in principle be used to provide health care interventions or research. The analytic framework outlined here suggests that the choice between medical technologies given existing information should be based on estimated mean cost-effectiveness. The uncertainty in the decision to adopt a medical technology should be quantified by assessing the value of further research [5].

Analysing a decision problem applying this analytic framework requires the following main tasks [13]:

1. Constructing a decision-analytic model appropriately representing the clinical decision problem under consideration.

2. A probabilistic analysis of this model in order to determine cost-effectiveness and characterise current decision uncertainty.

3. Estimating the value of additional information of research to reduce decision uncertainty.

Below, the different tasks of this analytic framework are summarised. A brief introduction to the methods of cost-effectiveness analysis is provided first, which basically covers tasks one and two in the analytic framework. This is followed by an outline of the value-of-information approach, which covers the third task of the analytic framework.

Cost-effectiveness analysis

Incremental cost-effectiveness ratios and net benefit

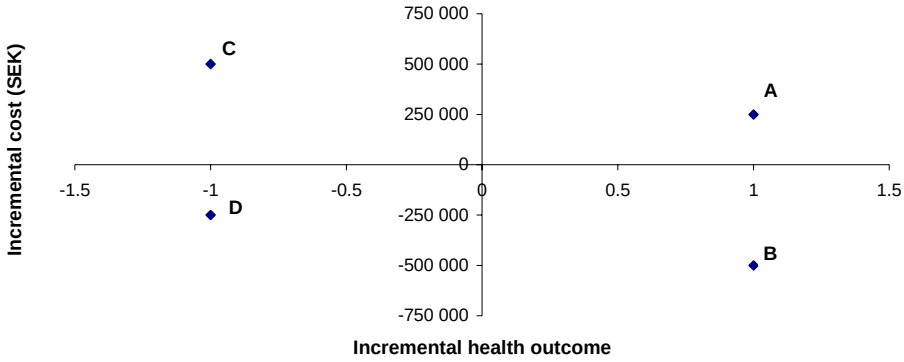
Economic evaluations aim to determine costs and health outcomes of relevant treatment strategies for a defined patient population [1]. The results are usually summarised as an incremental cost-effectiveness ratio (ICER), which in the case of two comparators is:

$$\mathrm{ICER} = \frac{(C_t - C_c)}{(E_t - E_c)} = \frac{\Delta C}{\Delta E},$$

where C_t (E_t) and C_c (E_c) are the estimated mean costs (health outcomes) of the treatment under investigation and a comparator, respectively. The ICER can be plotted on the cost-effectiveness plane, where the horizontal axis represents the difference in health outcomes between the treatment under investigation and the comparator, and the vertical axis represents the

difference in costs [14]. The cost-effectiveness plane is illustrated in Figure 1 where four hypothetical ICERs are plotted, representing the results of four different treatments (A to D) when compared with relevant alternatives. The ICER relates differences in costs to differences in health outcomes and decision rules can be applied in order to identify the most cost-effective treatment option of those being compared [15]. In the case of a treatment option being dominant (costing less and generating greater health outcomes than the alternatives with which it is compared), it is clearly cost-effective. This is illustrated by treatment B in Figure 1. Similarly, if a treatment option is dominated (costing more and generating less health outcomes), it is clearly not cost-effective. This is illustrated by treatment C in Figure 1. However, if a new treatment strategy generates additional health outcomes but at an extra cost, or similarly, generates less health outcomes but also reduces costs, the ICER is compared with those of other treatment strategies, or some notional threshold value which decision makers are willing to pay for an additional unit of health outcome, in order to determine the preferred option from those being compared [15]. This is illustrated by treatments A and D in Figure 1.

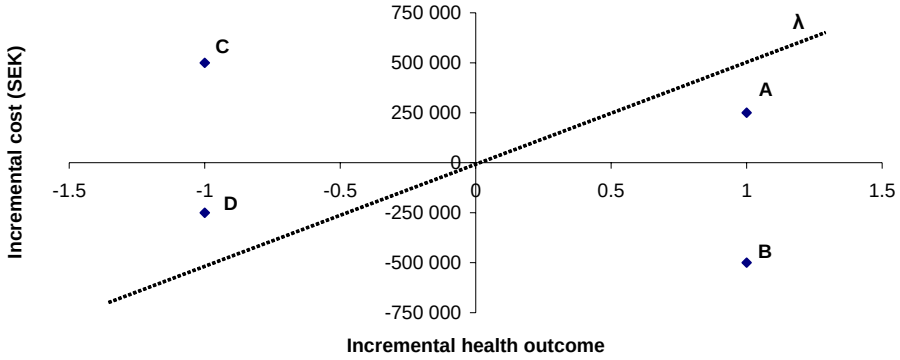
Figure 1. Illustration of the cost-effectiveness plane



A line, where the slope represents the threshold value, denoted λ, is superimposed on the cost-effectiveness plane in Figure 2. ICERs below and to the right of the line will be deemed cost-effective. Clearly a dominant treatment strategy, like treatment B, falls into this category. Figure 2 also illustrates that treatment A in this example appears to be cost-effective. ICERs above and to the left of the line will be deemed cost-ineffective. The

dominated treatment C is a clear example. Treatment D also appears cost-ineffective as the ICER is above the line.

Figure 2. Illustration of the cost-effectiveness plane with a notional threshold value (λ) representing the willingness to pay for a health outcome



The example above illustrates some important characteristics of the ICER. First, the ICER needs to be interpreted in association with the cost-effectiveness plane in order to determine whether a treatment strategy should be considered cost-effective or not [16]. Treatments A and D have numerically identical ICERs, but the interpretation is clearly different as treatment A is cost-effective whereas treatment D is not. A similar reasoning applies when comparing the ICERs of treatments C and B. This need not be a great concern when looking at the point estimates of the ICERs as it is often clear in which quadrant of the cost-effectiveness plane the ICER is located. However, this is more problematic when considering the uncertainty around the ICER as the joint distribution of incremental cost and health outcome may well span more than one quadrant, which can make it difficult to present this uncertainty. Second, a related issue is the problem with the statistical properties of the ICER. As a ratio statistic, the ICER tends to infinity when the difference in health outcome approaches zero, implying that the distribution of the ICER may not be statistically well behaved.

Rearranging the ICER to net monetary benefits [17] , or net health benefits [18], has been proposed as a solution to some of the problems with the ICER discussed above. The advantages with the net-benefit approach over the ICER

are that the interpretation of the results is unambiguous and that the problems with the statistical properties of a ratio are overcome. In this thesis, the approach of net monetary benefit is adopted, expressing costs and health outcomes in monetary terms. In the following, this is simply referred to as net benefit. Incremental net benefit (INB) for the investigated treatment strategy is thus defined as:

$$\mathrm{INB} = \lambda(\mathrm{E_t} - \mathrm{E_c}) - (\mathrm{C_t} - \mathrm{C_c}) = \lambda\Delta\mathrm{E} - \Delta\mathrm{C},$$

where λ is the threshold value, or willingness to pay, for a health outcome. It should be noted that the INB is the difference between the strategies net benefit (NB):

$$\mathrm{INB} = (\lambda\mathrm{E_t} - \mathrm{C_t}) - (\lambda\mathrm{E_c} - \mathrm{C_c}) = \mathrm{NB}_t - \mathrm{NB}_c.$$

As the INB is merely a rearrangement of the ICER, it is clear that using the ICER or the INB does not effect the decision whether a treatment strategy is cost-effective or not. If INB for the treatment strategy is positive, which is equivalent to the treatment strategy having the highest mean net benefit, it should in principle be adopted. It is important to note that the estimated ICER or INB will be associated with uncertainty relating to the precision with which they are estimated. A corollary is that decisions based on these results will also be uncertain and this thesis is partly concerned with methods to quantify this uncertainty and to determine whether it is useful to reduce it.

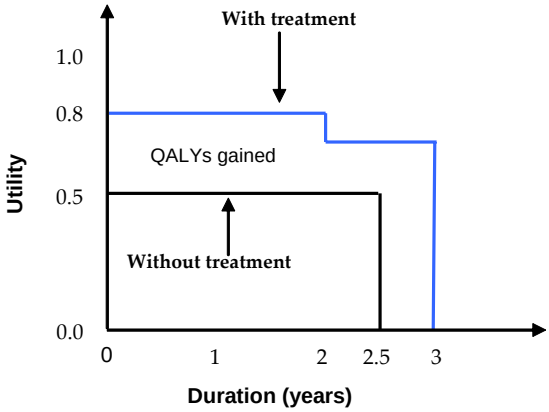
Costs and quality-adjusted life years

Methods concerning identification, measurement and valuation of costs and health outcomes are covered at length in standard textbooks on economic evaluation [1,2]. In this section, some basic concepts are introduced. Costs refer to the resources used, both in the health care system and other sectors in society. Resources within the health care system include clinical and other staff, capital equipment and buildings, and consumables such as pharmaceuticals. Examples of non-health service resources are time and travel of patients and productivity losses due to absence from work. The tasks of identifying, measuring and valuing costs are central in any economic evaluation. The perspective of the analysis is important when identifying the relevant costs to be considered in the analysis. Particular costs, such as travel

costs for patients, are relevant from a societal perspective, but not from the perspective of a health care provider. The measurement task is concerned with quantifying the actual resource use associated with an intervention. For a surgical procedure, this could encompass measuring the number of days in intensive care unit, number of surgeons, time in operation theatre and use of disposable equipment. There are different ways to measure resource use. The case study on early intervention in acute coronary syndrome collected resource use alongside a clinical trial and the case study on screening for abdominal aortic aneurysm utilised data available in clinical registries to measure resource use associated with surgical procedures. The valuation task is concerned with finding adequate unit costs, or prices, to be multiplied with the estimated resource use.

In the case studies, quality-adjusted life years (QALYs) are used as health outcome. The QALY combines quantity of life (mortality) and quality of life (morbidity) in a single measure. Quality-adjustment weights, where 0 represents dead and 1 represents full health, are used to weight the time spent in a health state with the health-related quality of life (HRQoL) associated with the health state. A QALY is therefore defined as one year of full health. The quality adjustment should reflect preferences for health states, i.e., the relative desirability, or utility, associated with different health states. A simple example illustrates the principles of calculating QALYs. At a point in time (time 0 in Figure 3), the HRQoL of a patient corresponds to a utility of 0.5. Without treatment, the health state of the patient is unchanged and the patient subsequently dies after 2.5 years as illustrated by the lower curve in the figure. Spending 2.5 years in this health state yields a total of 1.25 QALYs (2.5 years multiplied with a quality-adjustment weight of 0.5). With a hypothetical treatment at time 0, the HRQoL is improved, corresponding to a utility of 0.8 during the subsequent 2 years. The HRQoL deteriorates during the third year (corresponding to a utility of 0.7) after which the patient dies, as illustrated by the upper curve in the figure. Total QALYs for this patient are 2.30 [(2 years*0.8+1 year*0.7) = 2.30]. The treatment therefore results in 1.05 QALYs gained compared with no treatment.

Figure 3. Illustration of the principles for calculating quality-adjusted life years



An advantage with QALYs as an outcome measure is the possibility of comparing the results of cost-effectiveness analyses across disease areas as treatments principally affecting survival can be compared with treatments mainly having an impact on quality of life [1]. Furthermore, QALYs will more accurately represent the outcome of treatments that, for example, lead to gains in survival, but also result in side effects.

Decision-analytic modelling

Different approaches may be used for estimating costs and health outcomes of treatment strategies; individual-patient data from clinical trials, decision-analytic modelling, or a combination of the two. Although sometimes controversial [19-22], decision-analytic modelling has been used for a long time [23] and is increasingly accepted to establish cost-effectiveness for reimbursement decisions [7,24]. Recently, efforts have also been made to define good practice [25-27].

In the context of economic evaluation, Briggs and colleagues provide the following definition of decision-analytic modelling [28]:

> A decision-analytic model uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated. Based on the inputs into the model, the likelihood of each consequence is expressed in terms of probabilities, and each consequence has a cost and an outcome. It is thus possible to calculate the expected cost and expected outcome of each option under evaluation. For a given option, the expected cost (outcome) is the sum of the costs (outcomes) of each consequence weighted by the probability of that consequence.

The arguments for using decision-analytic modelling mainly focus on the fact that the requirements of economic evaluation prescribe that some kind of modelling will often be necessary when undertaking a cost-effectiveness analysis [29]. Some of these arguments are summarised below.

The methodological literature on economic evaluation is clear in that the required time horizon adopted for the analysis should be sufficiently long to reflect all the relevant differences in costs and health outcomes between treatment options. For many economic evaluations this will require a lifetime time horizon. This is particularly true when there are differences in mortality between the investigated treatments, where life-expectancy calculations require full survival curves to be estimated. Rarely, sufficient long-term individual-patient data will be available from a single source, such as a randomised trial or an observational study [28]. The decision-analytic model then provides a mean to extrapolate cost and health outcomes over time either by incorporating data from other sources or by expert opinion.

Decision-analytic models also provide a mean of comparing all relevant treatment options that could be used in clinical practice. In many cases, a single study, such as a randomised trial with selective comparators will not suffice as it is impossible to establish cost-effectiveness unless appropriate comparisons are made with the full range of competing alternatives. For example, recent methodological advances in the field of meta-analysis make it possible to estimate unobserved treatment effects from randomised trials comparing different treatments [30]. The results of such analyses can be combined with decision-analytic modelling in order to estimate costs and health outcomes for all relevant treatment options, and, at the same time, utilise all randomised evidence in the estimation of effectiveness.

Given that all available evidence should optimally be taken into account when estimating costs and health outcomes for a range of treatment strategies, synthesis of data is often required. Such synthesis could encompass the estimation of a parameter value of interest using data from several trials employing meta-analysis methods [31]. This type of synthesis is mostly seen for parameters concerning a relative treatment effect, but can also be employed for other parameters. A further important issue concerning evidence synthesis is that relevant data for a cost-effectiveness analysis is likely to be found in a wide range of sources. In fact, there may be circumstances where no trial has investigated the relevant comparators in the setting of interest. The decision-analytic model then provides a tool for bringing relevant data together and estimate cost-effectiveness.

A key argument for using decision-analytic modelling is the ability to indicate how uncertainty in the available evidence relating to a given decision-problem translates into decision uncertainty, i.e., the probability that a decision based on cost-effectiveness is the 'right' one [28]. The section below provides a brief overview of how probabilistic models can fully account for this uncertainty and the section outlining the value-of-information approach describes how this uncertainty can be quantified and used to determine the value of further research.

Uncertainty, variability and heterogeneity

An important task of the analytic framework is to characterise uncertainty surrounding each of the parameters in the model by assigning full probability distributions [32]. The distributions should represent the quality and quantity of evidence available for the parameters of interest and Monte Carlo simulation, or probabilistic sensitivity analysis, can then be used to propagate this parameter uncertainty through the model so that the imprecision of the cost-effectiveness results, and hence the decision based on cost-effectiveness, can be estimated [6].

When discussing uncertainty in decision-analytic modelling, it is important to distinguish between uncertainty, variability and heterogeneity [9,28]. The concept of uncertainty relates to parameters that have a definite value, but which cannot be known with certainty for a particular population of patients. More information, e.g., information from a clinical trial, can reduce

uncertainty and increase the precision with which a parameter is estimated. Therefore, parameters that should be characterised as probability distributions are those that (in principle) can be sampled in order to increase the precision with which they are estimated [32,33]. Examples include probabilities of certain events, such as death or non-fatal cardiovascular events, resource use and quality of life associated with the treatment strategies under evaluation. The results of probabilistic sensitivity analysis are often summarised in cost-effectiveness acceptability curves, showing the proportion of iterations of the Monte Carlo simulation that a medical technology is cost-effective [34-36]. However, to fully account for decision uncertainty the probability of making the wrong decision based on cost-effectiveness needs to be combined with the consequences of making the wrong decision. This is the key principle of value-of-information analysis discussed in detail below. An important note in relation to probabilistic analysis is that for decision models in which there is a multi-linear relationship between inputs and outputs, the correct calculation of expected costs and health outcomes will need the full uncertainty around parameters to be expressed. Therefore, the probabilistic analysis of the model also ensures adequate estimates of expected net benefit [8,28].

Variability refers to natural variation between individuals outcomes, even when they have the same observed characteristics [9,28]. It may be known with certainty that a probability of a specific event is 0.20 in a defined population, indicating that 20 out of 100 patients will experience the event. However, we do not know in advance which particular 20 patients out of the 100 that will experience the event [28]. Variability cannot be reduced by acquiring more information.

Heterogeneity refers to differences in parameters between patients who have different observed characteristics, such as gender, age and co-morbidity. It is possible to account for heterogeneity in economic evaluations by estimating cost-effectiveness for individuals with different characteristics. Event-based modelling provides a mean to accomplish this and is perhaps best described as a combination of statistical analyses and decision-analytic modelling. Statistical analyses of individual-patient data are used to determine event rates, costs and health-related quality of life for a large number of subgroups defined by the covariates included in the statistical equations. The cost-effectiveness of these subgroups is then extrapolated from the statistical analyses by employing a decision-analytic model [28]. Although, some recent

publications are available [37,38], this approach to cost-effectiveness analysis is still under development.

The value-of-information approach

Another important task of the analytic framework is concerned with quantifying the costs of decision uncertainty by establishing the expected value of perfect information and perfect partial information. Although the methods of value of information are not new [3,39] and have been applied in several disciplines [40], they appeared in the literature of economic evaluation in the late 1990s [5,41-44]. The outline below follows the principles set out by Claxton in 1999 [5], with refined technical details published in 2004 by Ades and colleagues [45].

Decisions about the adoption of medical technologies are associated with uncertainty due to the uncertainty in the estimated cost-effectiveness. The expected costs of this uncertainty can be quantified and are determined by the probability that a treatment decision based on existing information will be wrong and the consequences if the wrong decision is made [5]. Information from additional research is valuable for health care decision makers because it reduces the uncertainty surrounding an adoption decision. If society is willing to pay a certain amount of money for a QALY gained, referred to as λ above, the expected cost of uncertainty represents the amount society is willing to pay to eliminate the uncertainty associated with the adoption decision [5]. The expected cost of uncertainty can also be interpreted as the expected value of perfect information (EVPI) since if we were in a position of perfect information the possibility of making the wrong adoption decision is eliminated.

The value of information for the decision

Formally, we define $B(t, \theta)$ as the net benefit of strategy *t* (t = 1, 2, representing a treatment and control strategy, respectively) if the parameters in the decision-analytic model employed to estimate cost-effectiveness take the value θ. The optimal decision given current information is given by choosing the strategy with the highest mean net benefit: $\max_t E_\theta B(t, \theta)$, which will maximise the expected net benefit. This states that given the estimated mean costs and

QALYs of the treatment and control strategies, the treatment strategy should be adopted if the mean INB for the treatment strategy is positive.

As outlined by Ades et al., the true values of θ are not known but if they were known, it would be possible to maximise over *t*, $\max_t B(t, \theta)$, to obtain a value of an optimal decision at these known values of θ [45]. As θ is not known the expected net benefit of a decision taken with perfect information is found by averaging this expression over the joint distribution of θ: $E_\theta \max_t B(t, \theta)$. EVPI is thus the net benefit given perfect information minus the net benefit given current information:

$$\text{EVPI} = E_\theta \max_t B(t, \theta) - \max_t E_\theta B(t, \theta).$$

Employing non-parametric Monte-Carlo simulation, the net benefit given perfect information, i.e., $E_\theta \max_t B(t, \theta)$, is derived by taking the average of the maximums in each iteration of the Monte Carlo simulation [41,45,46]. This is shown in Table 1, which illustrates how the EVPI is established using simulation methods. The results of a hypothetical Monte Carlo simulation running only 5 iterations are shown in the table. It should be noted that in real applications several thousand iterations are normally used.

The net benefit of each treatment strategy, which is a function of the uncertain parameters in the decision-analytic model, is shown in columns two and three. The results in columns two and three thus reflect our current knowledge about costs and health outcomes (summarised as net benefit) of the two treatment strategies. With imperfect information of the parameters in the decision-analytic model, and therefore also the net benefit of treatment and control, the decision to adopt the treatment or control strategy have to be based on the mean net benefits. In this hypothetical example the treatment strategy has the highest mean net benefit (135 000 SEK) compared with control (120 000 SEK) and would be the optimal adoption decision as it generates a gain in net benefit of 15 000 SEK compared with the control strategy.

In a theoretical position of perfect information, we would know how the net benefit resolves in each of the iterations of the Monte Carlo simulation. With this perfect information the decision no longer has to be based on the mean net benefit. Rather, the right decision can be made in each of the iterations. In this simple example, the control strategy would be the preferred choice in iterations 2 and 5. The net benefit with perfect information is shown in

column 5 and the improved net benefit from choosing with perfect information, rather than based on the mean, is the estimated EVPI for the decision to adopt the treatment strategy and is found in the last column of the table.

Table 1. Illustration of the principles for establishing the expected value of perfect information

Iteration of the probabilistic analysis	Net benefit Treatment	Net benefit Control	Incremental net benefit Treatment	Net benefit with perfect information	Improved net benefit with perfect information
1	150 000	120 000	30 000	150 000	0
2	120 000	130 000	-10 000	130 000	10000
3	130 000	110 000	20 000	130 000	0
4	140 000	100 000	40 000	140 000	0
5	135 000	140 000	-5 000	140 000	5000
Mean	135 000	120 000	15 000	138 000	3000

The estimated EVPI is the maximum value that should be placed on additional information to inform the treatment choice for an individual patient. However, any information acquired can be used to inform the policy decision for all eligible patients entering the same decision problem now and in the future. By estimating the number of patients (N) entering the decision problem in each period (t) and applying a discount rate (r) the EVPI for the population can be established [5]:

$$\text{Population EVPI} = \text{EVPI}_{\text{patient}} * \sum_{t=1}^{t} \frac{N_t}{(1+r)^t} .$$

This shows the EVPI for an individual patient multiplied by a constant. The constant is the estimated number of patients facing this decision problem during the chosen period (t), sometimes referred to as the effective population.

The estimated EVPI for the decision is the total value of information, or cost of uncertainty, associated with the adoption decision. Economic principles can then be used to decide whether more information should be collected to inform this decision problem. The total EVPI can be compared with the cost of collecting further information in order to assess whether it is sensible to demand more information. If the cost of collecting further information is less than the estimated EVPI it is potentially worthwhile to undertake further

studies. However, the EVPI for the decision only provides a 'first hurdle' when deciding if it is cost-effective to collect further information. More precise guidance is needed to determine what type of information, e.g., a clinical trial or and observational study, will be needed to reduce the uncertainty in the adoption decision. More precise guidance on further research can be established by estimating the EVPI for particular model parameters.

The value of information for parameters

The EVPI for particular model parameters (or sets of parameters) can also be established. Following the same notation as above, $E_{\theta_I} \max_t E_{\theta|\theta_I} B(t, \theta)$ is the expected value of a decision made with perfect information about θ_I, where θ_I is a subset of θ [45]. The estimation is similar to that of EVPI for the decision, but rather than assuming that we have perfect information about all parameters in each of the iterations of the probabilistic assessment, it is now assumed that we only have perfect information about the parameter(s) of interest (θ_I). The expected value of partial perfect information (EVPPI) is thus given by:

$$\text{EVPPI} = E_{\theta_I} \max_t E_{\theta|\theta_I} B(t, \theta) - \max_t E_\theta B(t, \theta).$$

This is the difference between the expected net benefit of a decision made with perfect information about θ_I and the current optimal decision [45]. A complicating issue when estimating the EVPPI is that it normally requires additional simulations in order to determine the expected net benefit given a certain value of θ_I. Therefore, for this analysis a value from the distribution(s) of θ_I is drawn and the uncertainty in the remaining parameters is propagated through the model. The expected net benefits from this exercise is the results of one iteration when estimating the EVPPI for θ_I. This is then repeated for a sufficient number of values from the distribution of θ_I. It should be noted that the reason the additional simulation is required is that a Markov model is not linear in the complementary set of parameters, i.e., all the parameters except the one(s) of interest, thus the need for a two-level Monte Carlo simulation [45,46]. If a model is linear in the complementary sets of parameters it is enough to sample from the distribution of θ_I and then apply the mean values from the complementary parameters.

With information on EVPPI it is possible to identify the parameters contributing most to the decision uncertainty. In a similar way to overall EVPI, the cost of acquiring more information about a specific parameter can be compared with the EVPPI for that parameter. If the EVPPI is higher than the cost of acquiring more information it is potentially worthwhile to investigate the parameter further. This has important implications for prioritising research as specific areas of research can be identified. Moreover, different parameters are likely to require different study design. Some parameters, such as the relative treatment effect would probably need a randomised design, whereas other parameters could be investigated by cohort studies (baseline risk) or surveys (utilities).

Efficient research design and the value of sample information

If the EVPPI for particular parameters is higher than the estimated costs of investigating the parameters, further data collection is potentially worthwhile. However, decision makers still need to consider how much information that should be acquired (e.g., sample size) and how the study should be set up. These issues are concerned with efficient research design. The objective is to establish the optimal design of a study, conditional on the uncertainty in the parameter the study aim to inform, and the cost of conducting the study. The analyses require substantial simulation and detailed methods are provided by Ades and colleagues [45].

The general principle is to establish the expected value of sample information (EVSI), which is the difference between the expected value of a decision made after new data have been acquired and the expected value of a decision made with current information. The EVSI can then be compared with the cost of acquiring the new data in order to determine the optimal design of a new study.

3. INTRODUCTION TO THE CASE STUDIES

This chapter introduces the case studies, which form the empirical basis of this thesis. The aim is to provide a brief introduction to the clinical decision problems and an overview of the methods employed to evaluate cost-effectiveness and value of further research. The case studies were selected on the basis that they are policy-relevant investigations in the same disease area and involve different types of methodological challenges. As mentioned previously, details of methods and material, such as comprehensive modelling methods, statistical analyses and data sources are found in the five papers and in the appendix of this thesis.

Screening for abdominal aortic aneurysm

The prevalence of abdominal aortic aneurysm (AAA) is above 5 percent, using a definition of aortic diameter of 3 cm or more [47], and causes about 2 percent of all deaths [48] in men over the age of 65. Only about 35 percent of the individuals suffering from a ruptured AAA reach the hospital and undergo surgery. Allowing for operative mortality, the estimated total mortality from a ruptured AAA is around 75 percent [49]. Hence, even a major improvement in peri- and postoperative mortality would have a modest impact on total mortality. Screening for AAA has been discussed [50], evaluated [51], and recommended [52,53] as a solution. Randomised controlled trials, including individuals between 65 and 80 years of age, have shown that screening can reduce AAA-related mortality in men [51,54,55]. This outcome was not clearly established in a randomised trial including men between 65 and 83 years of age [56]. Studies investigating the cost-effectiveness of screening for AAA have differed in their results, with some investigators reporting a low cost [57] and others a substantially higher cost per gained health outcome [58].

As both the prevalence of the disease and the mortality from elective surgery increase with age, the age of 65 has been suggested as appropriate for a screening programme. Moreover, follow-up of screened individuals show that a negative screening at 65 practically excludes the risk of an aneurysm later in life [59]. Furthermore, screening of women for AAA has shown no effect on AAA-related mortality [55]. Therefore, the screening programme

considered in this work is concerned with 65-year-old males. The long-term cost-effectiveness of such a screening programme has not been established and it is unclear whether such a screening programme should be recommended or not.

At the time of the initiation of this evaluation in 2004, no organised screening programme for AAA existed in Sweden. Screening for AAA was subjected to an early assessment in 2003 by the governmental agency the Swedish Council on Technology Assessment (SBU). The first technology brief was based on the existing literature, including three large randomised clinical trials of which none had been performed in Sweden, and the brief concludes [60]:

> There is strong scientific evidence (Evidence grade 1)* that screening reduces abdominal aortic aneurysm-related mortality in men. Limited scientific evidence exists (Evidence grade 3)* with regard to the method's cost- effectiveness. No evaluation study has been conducted in Sweden concerning screening for abdominal aortic aneurysms. No randomised study has examined total effects and costs of screening all men, when screening began at the age of 65. A number of ethical considerations require further examination. Any kind of screening program for abdominal aortic aneurysms that is contemplated in Sweden should fall within the scope of a scientific study that evaluates all potential consequences.
>
> *Grading of the level of scientific evidence for conclusions. The grading scale includes four levels; Evidence grade 1 = strong scientific evidence, Evidence grade 2 = moderately strong scientific evidence, Evidence grade 3 = limited scientific evidence, Evidence grade 4 = insufficient scientific evidence.

Clearly, an organised screening programme was not recommended in routine clinical care in 2003 by SBU. The main reason for this conclusion appears to be the lack of evidence of costs and effectiveness of a screening programme in a Swedish setting with a particular design (inviting 65-year-old males for a one-time screening). According to SBU, any kind of screening programme for AAA set up in Sweden should fall within the scope of a scientific study where all costs and consequences of the programme are investigated.

A disease progression Markov model was constructed in order to model the natural history of the disease and the impact of the natural history of the disease with a screening programme (Paper I). With the screening programme, all men were invited to an ultrasound investigation, which will result in a proportion of men with an AAA being detected. Subsequent management comprised surveillance for small- and medium-sized aneurysm, whereas individuals with large AAAs were offered elective surgery. The

model was populated with data from a wide range of sources in order to estimate costs and health outcomes over a lifetime time horizon for a Swedish setting, with and without a screening programme. A value-of-information analysis was performed in order to establish whether further research should be recommended for this decision problem (Paper II). The value of information was established employing the methods of simulation outlined in chapter 2.

Early intervention in acute coronary syndrome

Non-ST-elevation acute coronary syndrome (NSTE-ACS) represents a major health burden to health care systems and patients face a substantial risk of mortality and cardiovascular events. Although evidence suggests that the use of a strategy of early angiography with a view to revascularisation in the management of patients with NSTE-ACS is associated with an increased risk of myocardial infarction or death during the index hospitalisation, the reduced risk subsequently implies an overall reduction in the risk of myocardial infarction or death [61]. The 5-year follow-up of the third Randomised Intervention Trial of unstable Angina (RITA 3) confirmed these findings showing that an early interventional strategy reduced the risk of the composite endpoint of death or myocardial infarction [62]. Furthermore, it has been shown that an early interventional strategy improves health-related quality of life at one year but also leads to increased costs when compared to a conservative strategy [63,64]. In order to establish whether an early interventional strategy should be recommended for widespread implementation, its cost-effectiveness needs to be assessed to determine whether the gain in health outcomes justifies any increased costs.

Present clinical guidelines suggest that early interventional strategy is performed in patients at intermediate (early catheterisation) or high risk (urgent catheterisation) [65]. These guidelines are based on clinical risk and do not consider cost-effectiveness. No guidelines concerning further research into the cost-effectiveness of an early interventional strategy in the UK have been identified. Furthermore, data on the utilisation of an early interventional strategy in the UK at present has not been identified. Summary data indicate that the percentage of patients assigned an early interventional strategy is increasing, although the exact figure for the UK is unclear [66].

Individual-patient data from the RITA 3 trial was used for the economic evaluation. Data collected in the trial included information on clinical endpoints (e.g., cardiovascular death and myocardial infarction), costs and health-related quality of life. In the present analysis an event-based modelling approach was used (Paper III).

Rates of cardiovascular death or myocardial infarction, costs and health-related quality of life were estimated using statistical analyses and extrapolated to the relevant lifetime time horizon within a decision-analytic model. A two-stage model; a short-term decision tree, representing the index hospitalisation (defined as time from randomisation to hospital discharge), and a long-term Markov model, representing the time after the index hospitalisation was employed. Costs and QALYs were estimated over a lifetime time horizon for a UK setting from the perspective of the NHS. Since baseline risk is a potentially important predictor of both cardiovascular events and the effectiveness of early intervention, the model investigated cost-effectiveness in patients with different risk profiles at randomisation [62]. Secondary analyses considered whether cost-effectiveness results change when clinical results from a meta-analysis of trials were used in the model and when treatment effect was allowed to vary with baseline risk.

Endarterectomy in patients with asymptomatic carotid artery stenosis

It is well known that patients with a symptomatic and tight carotid artery stenosis has a high risk of stroke during the first 3 to 6 months after the warning symptoms and that this risk can be ameliorated with prompt carotid artery surgery [67] in a cost-effective way [68]. Patients with a substantial (e.g., 60-99 percent) asymptomatic carotid artery narrowing are also at increased risk of suffering a disabling or fatal stroke in the carotid artery territory of the brain. Although endarterectomy can remove arterial narrowing and reduce the long-term risk of stroke in patients with asymptomatic carotid artery stenosis, the procedure involves some immediate risks of perioperative death or stroke. Hence, to establish clinical effectiveness of carotid endarterectomy in addition to best medical treatment in patients with an asymptomatic lesion, the procedural risks and long-term benefits need to be considered, and compared with a treatment strategy of best medical treatment alone. Moreover, long-term costs of the treatment options need to

be established when deciding on the optimal treatment strategy for these patients. Randomised trials have shown that endarterectomy can reduce the long-term risks of stroke in patients with an asymptomatic lesion [69,70]. Furthermore, it has been shown that endarterectomy could be considered cost-effective in a North American setting [71], but cost-effectiveness has not been investigated in a European setting and it is unclear whether the results from North America are readily transferable to Sweden.

In recent years, the number of carotid endarterectomies performed in patients with an asymptomatic lesion has increased in Sweden, although there is large variation in clinical practice between centres [72]. Guidelines on the management of patients with an asymptomatic lesion have been issued by the National Board of Health and Welfare in Sweden [73]. Based on the North-American study mentioned previously [71], it is noted in the guidelines that carotid endarterectomy is associated with a cost per QALY gained below 100 000 SEK when compared with a strategy of best medical treatment alone. However, in the summary of the guidelines the incremental cost-effectiveness ratio of endarterectomy compared with best medical treatment is said to be moderate to high. In the subsequent priority ranking of stroke-related interventions, endarterectomy for asymptomatic carotid artery stenosis is ranked as a "6" on a scale of 1 to 9, where "1" indicates the highest priority and "9" the lowest. No guidelines on further research into the cost-effectiveness of carotid endarterectomy seem to exist.

The recent international randomised Asymptomatic Carotid Surgery Trial (ACST) investigated the efficacy of carotid endarterectomy and individual-patient data from the Swedish patients was used for the present analysis. A Markov model was employed in order to estimate cost-effectiveness of carotid endarterectomy in addition to best medical treatment compared with best medical treatment alone in a lifetime time horizon for a Swedish setting from a societal perspective (Paper IV). Data from a range of sources was employed in the analysis including individual-patient data on the Swedish patients randomised in the ACST trial. Cost-effectiveness was estimated for patients at different ages and for men and women separately. A value-of-information analysis was performed in order to establish the value of further research following the methods of simulation outlined in chapter 2 (Paper V).

Summary of the case studies

An overview of the decision problems investigated in the case studies is given in Table 2. All case studies are concerned with treatment strategies in cardiovascular disease. Furthermore, all case studies compare an active intervention strategy with a conservative approach, where the main aim of the active interventions is to reduce the future risk of cardiovascular events. In the case studies of carotid endarterectomy and early intervention in acute coronary syndrome, the two main strategies for handling these patients are compared, and hence the evaluations adhere to the methodological position of comparing all relevant treatment strategies. In the study investigating screening for abdominal aortic aneurysm, the comparison of one particular design of a screening study is clearly a simplification as different designs of the screening programme could have been investigated, and compared in the analysis. As shown in Table 2, the investigated treatment strategies are used in clinical practice to a various extent. Furthermore, official recommendations or guidelines for the investigated treatment strategies are available, but only for screening for abdominal aortic aneurysm have clear guidance based on cost-effectiveness and recommendations for further research been identified.

Key methodological aspects of the case studies are summarised in Table 3. The two Swedish studies are evaluated from a societal perspective, which is the recommended perspective by governmental bodies in Sweden. In the UK study, a health-service perspective is used. As noted previously, the normative question of which perspective is the 'correct' one is beyond the scope of this thesis. However, it is important to bear this difference in perspective in mind when interpreting the results. Finally, the case studies involve different types of methodological challenges. In screening for abdominal aortic aneurysm, various data sources are synthesised in order to build a disease progression model where no clinical trial exists for the relevant setting. This is contrary to early intervention in acute coronary syndrome, where the evaluation is based on, and stays close to, a large clinical trial. In the case study on endarterectomy in patients with asymptomatic carotid artery stenosis, an attempt is made to combine the approaches from the two previous case studies.

Table 2. Overview of the decision problems investigated in the thesis

	Screening for abdominal aortic aneurysm	**Early intervention in acute coronary syndrome**	**Endarterectomy in patients with asymptomatic carotid artery stenosis**
	Papers I and II	**Paper III**	**Papers IV and V**
Strategy under evaluation	Screening programme	Early interventional strategy	Carotid endarterectomy
Description of strategy under evaluation	Invitation of men to ultrasound screening with surveillance and surgery conditional on size of the aorta	Early angiography with management guided by angiographic findings	Carotid endarterectomy in addition to best medical treatment
Comparator	No screening programme	Conservative strategy	Best medical treatment alone
Patient population	All 65-year-old men	Patients presenting with non-ST-elevation acute coronary syndrome	Patients diagnosed with an asymptomatic carotid artery stenosis
Status of strategy under evaluation at time of evaluation	Not used in clinical practice	Used in clinical practice for some patients but unclear to what extent	Used in clinical practice for some patients with geographical variation
Recommendations available at time of evaluation	Do not adopt a screening programme, further research needed*	Clear clinical guidance on adoption, no guidance on further research**	Vague guidance on adoption, no guidance on further research***

* Issued by the Swedish Council on Technology Assessment in Health Care (SBU) [60].
** Issued by the European Society of Cardiology [65].
*** Issued by the National Board of Health and Welfare in Sweden [73].

Table 3. Summary of key methodological aspects of the case studies

	Screening for abdominal aortic aneurysm **Papers I and II**	**Early intervention in acute coronary syndrome** **Paper III**	**Endarterectomy in patients with asymptomatic carotid artery stenosis** **Papers IV and V**
Analyses performed	Cost-effectiveness Value of information	Cost-effectiveness	Cost-effectiveness Value of information
Perspective	Societal	Health service	Societal
Setting	Sweden	UK	Sweden
Main outcome	Cost per QALY EVPI, EVPPI	Cost per QALY	Cost per QALY EVPI, EVPPI
Time horizon	Lifetime	Lifetime	Lifetime
Data sources	Primary data collection, published sources and registry data	Individual-patient data from a clinical trial and published sources	Individual-patient data from a clinical trial, published sources and registry data
Methods	Disease progression decision-analytic Markov model populated with data from several sources	Two-stage model (decision tree and Markov model) populated with trial data employing statistical modelling (event-based modelling)	Markov model populated with data from several sources, including statistical analyses of trial data
Methodological challenges	Synthesising various data sources to build a disease progression model for the relevant setting	Combine statistical and decision-analytic modelling to account for heterogeneity in cost-effectiveness	Perform value-of-information analysis when accounting for heterogeneity

4. RESULTS OF THE CASE STUDIES

This chapter provides the main results of the case studies and focuses on cost-effectiveness and value of information. Results of statistical analyses and analyses performed to assess model validity are found in the appendix.

Screening for abdominal aortic aneurysm

In the base-case analysis, the mean incremental costs and mean incremental QALYs for the screening programme over a lifetime time horizon was €194 and 0.020, respectively, yielding a cost per QALY gained of €9 700 for a screening programme compared with no screening. The results of the scenario analyses showed that the cost-effectiveness results were fairly robust to the key assumptions employed in the model (Table 4).

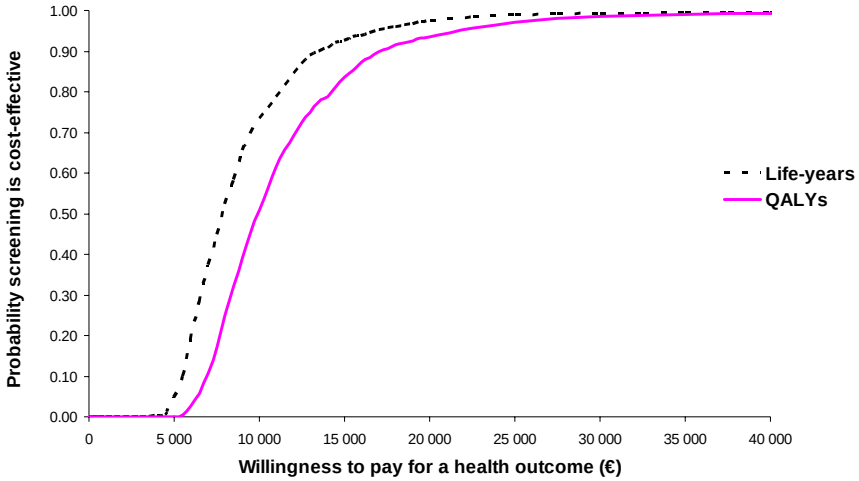
Table 4. Cost-effectiveness of a screening programme with different scenarios

Scenario	Cost/life year	Cost/QALY
Base-case analysis	7 760	9 700
Discount rate costs 3 % and health outcomes 0 %	5 550	7 065
Discount rate costs 6 % and health outcomes 1.5 %	6 490	8 230
Decrement (0.1) in quality of life Post op	NA	13 800
Decrement (0.071) in quality of life when diagnosed	NA	16 710
Standard mortality instead of estimated mortality for non-AAA related mortality of AAA individuals	14 250	18 000
Sensitivity ultrasound investigation 80 %	9 620	12 170
Inclusion of cost of added life years	29 800	37 800

Results are reported as cost per gained health outcome for screening compared with no screening. NA=not applicable.

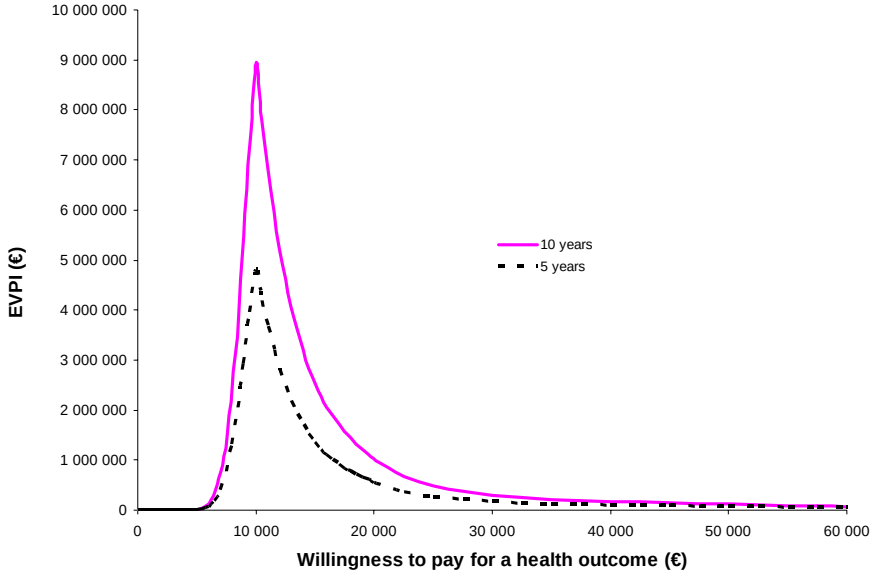
The probability of screening being cost-effective for different willingness to pay for a health outcome is shown in the cost-effectiveness acceptability curves in Figure 4. As seen in the figure, the probability of screening being cost-effective is high even at low willingness-to-pay values for a health outcome.

Figure 4. Cost-effectiveness acceptability curves for screening



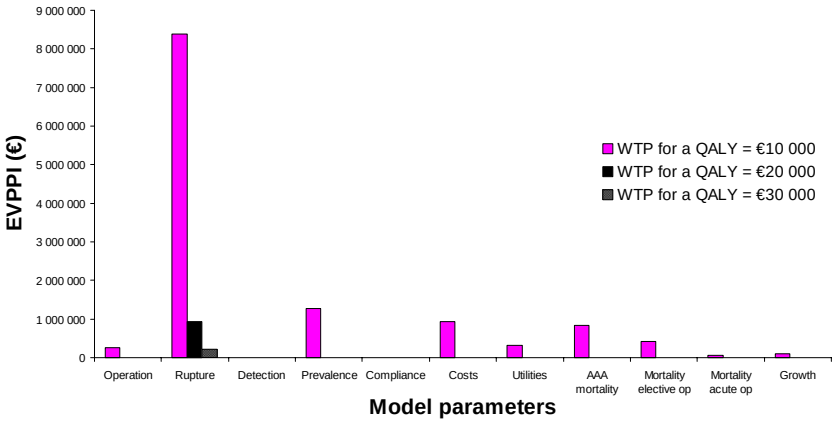
The results of the value-of-information analysis are shown in Figures 5 and 6. The calculations are based on a yearly population of 40 000 men, which approximately correspond to the number of men turning 65 each year in Sweden. The expected value of perfect information (EVPI) for the decision to adopt a screening programme is shown in Figure 5 for a time horizon of 5 and 10 years, respectively. Using a willingness to pay for a QALY of €50 000, the EVPI is €115 000 when employing a time horizon of 10 years. Corresponding figure for a time horizon of 5 years is €60 000.

Figure 5. Expected value of perfect information for the decision to adopt a screening programme



The expected value of perfect partial information for model parameters (EVPPI) is shown in Figure 6 employing a time horizon of 10 years. The parameter associated with the highest value of information was the probability of rupture for different sizes of the abdominal aorta. It should be noted that for illustrative purposes the results in Figure 6 are for low willingness-to-pay values for a QALY. Employing conventional willingness-to-pay values, the EVPPI for the probability of rupture is low (€70 000 if willingness to pay is €50 000).

Figure 6. Expected value of perfect information for model parameters



Operation: probability of getting an operation when an AAA ruptures. **Rupture**: probability of rupture for a Small, Medium, and Large AAA. **Detection**: probability of opportunistic case finding. **Prevalence**: prevalence of AAA ≥ 3 cm and proportion of AAA in each size group. **Compliance**: compliance with the invitation to the screening programme. **Costs**: cost of acute and elective surgery. **Utilities**: utilities different age groups. **AAA mortality**: long-term survival prognosis of AAA individuals. **Mortality elective op**: mortality within 6 months of an elective operation. **Mortality acute op**: mortality within 6 months of an emergency operation. **Growth**: probability of growing from Small to Medium and from Medium to Large AAA. WTP: willingness to pay.

In summary, the results of the cost-effectiveness analysis show that inviting 65-year-old males to an ultrasound investigation will yield a gain in QALYs at a cost likely to be considered acceptable. As long as decision makers place a higher value than €9 700 on a QALY, it is cost-effective to adopt a screening programme. The results from the probabilistic analysis showed that screening has a high probability of being cost-effective. Given the information available on the overall cost–effectiveness of screening, it appears unlikely that any further research regarding this decision problem is worthwhile.

Early intervention in acute coronary syndrome

Statistical analyses were used in order to estimate event rates, costs and health-related quality of life from the trial data. The results shown in Table 5 indicate that early intervention is associated with an increased risk of cardiovascular death or myocardial infarction during the index hospitalisation compared with the conservative strategy (odds ratio 1.52). It is also shown in Table 5 that after the index hospitalisation, early intervention is associated

with a decreased risk of cardiovascular death or myocardial infarction (hazard ratio 0.621). The estimated event rates from the statistical models were converted to probabilities, which were employed in the decision-analytic model. In a similar way, costs and health-related quality of life were established and incorporated into the decision-analytic model.

To investigate potential differences in costs and QALYs in patients with different risk profiles, the cost-effectiveness of an early interventional strategy was estimated using the individual covariate patterns of each patient in RITA 3. These are presented as a distribution of mean cost-effectiveness across the sample of trial patients in Figure 7. In RITA 3, a multivariate predictive model for death or myocardial infarction within 5 years was used to calculate a risk score defining quartiles of risk (risk groups 1 to 4) [62]. Because of the much higher event rate in the top quartile, this quartile was then further subdivided into equal-sized top two-eights of risk (risk groups 4a and 4b) [62]. The distribution of cost-effectiveness within these clinical risk groups is also shown in Figure 7. Furthermore, a detailed presentation of cost-effectiveness of the characteristics of the patients with the median risk score in each of these five risk groups is shown in Table 6.

Table 5. Estimated short- and long-term risks of the composite endpoint of cardiovascular death or myocardial infarction

	Odds ratio of composite endpoint of myocardial infarction or cardiovascular death during the index hospitalisation, n=1808		**Hazard ratio of composite endpoint of myocardial infarction or cardiovascular death from hospital discharge until end of trial, n=1756**	
Explanatory variables	Odds ratio	95% confidence interval	Hazard ratio	95% confidence interval
Age (for every 10 years over 60)	1.731	1.262-2.374	1.777	1.499-2.108
Diabetes			1.905	1.359-2.672
Previous myocardial infarction			1.471	1.087-1.990
Smoker			1.651	1.207-2.258
Pulse (for every 5 beats per minute)			1.062	1.012-1.114
ST depression			1.423	1.067-1.913
Angina (grade 3 or 4)	1.893	1.086-3.299	1.323	0.988-1.771
Male			1.372	1.007-1.869
Left bundle branch block			1.977	1.169-3.344
Randomised to early interventional	1.520	0.864-2.675	0.621	0.464-0.830
Ancillary parameter*			0.579	0.505-0.664

Coefficients show proportionate increase in risk over baseline event rates where the latter relates to rates in patients in the conservative arm without any of the risk factors included in the analysis.

*Shape parameter in the Weibull model where a value less than (above) 1 indicates a decreasing (increasing) hazard over time.

Figure 7. Cost-effectiveness based on estimated mean costs and QALYs, with and without early intervention, for patients in RITA 3 (n=1807)

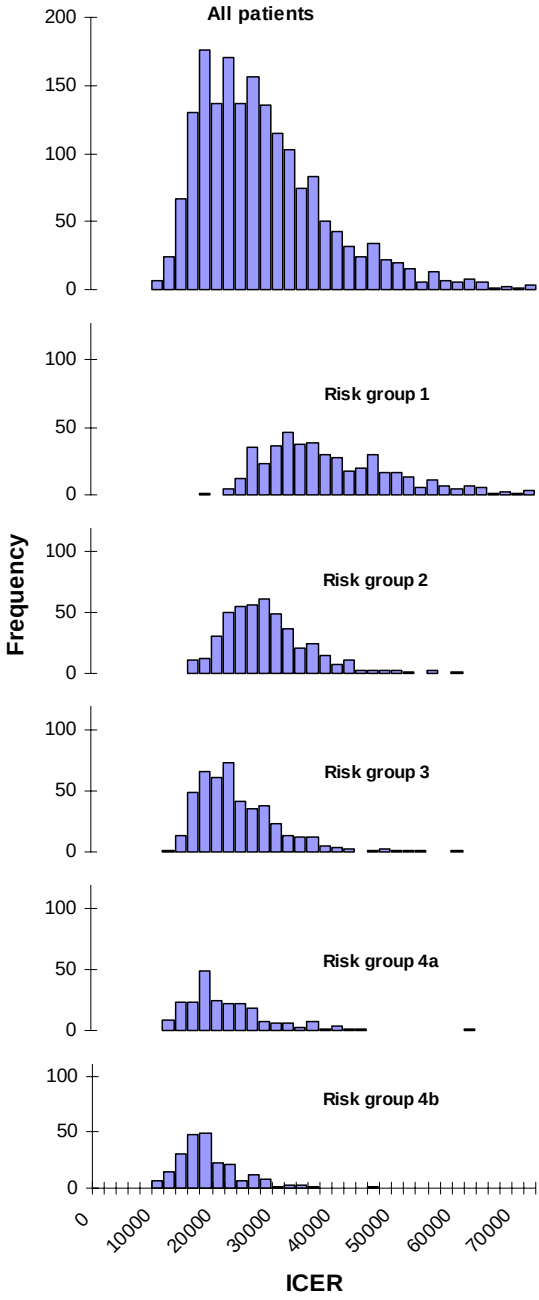
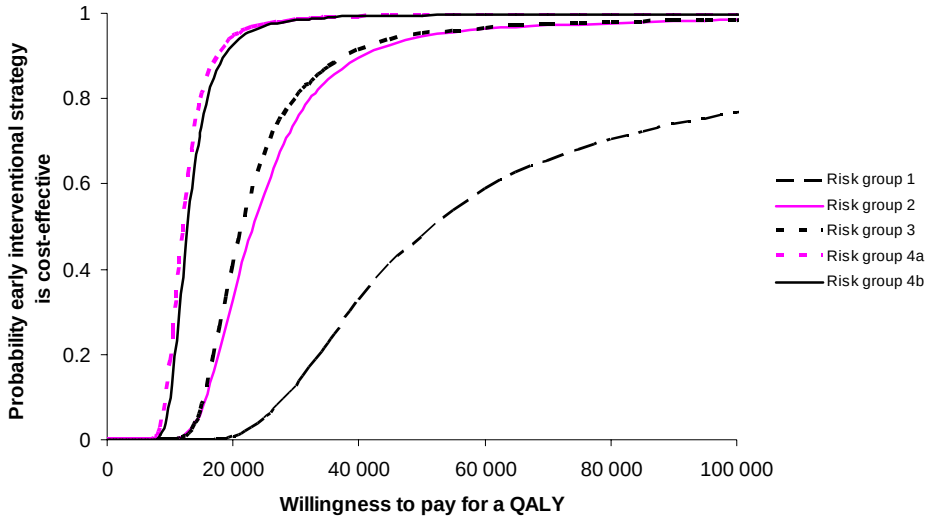


Table 6. Cost-effectiveness results by patient risk profile

	Risk group 1	Risk group 2	Risk group 3	Risk group 4a	Risk group 4b
Age	45	52	52	61	66
Diabetes	No	No	No	No	Yes
Previous myocardial infarction	No	No	Yes	Yes	Yes
Smoker	No	Yes	No	Yes	No
Pulse (beats per minute)	72	82	82	87	97
ST depression	No	No	Yes	Yes	Yes
Angina (grade 3 or 4)	Yes	No	Yes	No	No
Male	Female	Male	Male	Male	Male
Left bundle branch block	No	No	No	No	No
Incremental cost (£)	4 885	4 898	6 045	6 538	6 530
Incremental QALY	0.0909	0.2134	0.2834	0.5468	0.5122
ICER (£)	53 760	22 949	21 325	11 957	12 750

The proportion of iterations of the probabilistic analysis with a positive incremental net benefit for the early interventional strategy is shown in the cost-effectiveness acceptability curves for the five specified patient characteristics representing each risk group (Figure 8).

Figure 8. Cost-effectiveness acceptability curves for the early interventional strategy



The estimated effectiveness and cost-effectiveness for the alternative scenarios around the effectiveness of the early interventional strategy are shown in Tables 7 and 8 for the 5 specified patient characteristics representing each risk group. The pooled treatment effect (both in the index and follow-up period) from the meta-analyses of 8 trials was similar to the treatment effect observed in RITA 3. Hence, the estimated cost-effectiveness of an early interventional strategy using this alternative scenario is similar to that observed when using the treatment effect estimated in RITA 3 (Table 7).

Table 7. Cost-effectiveness results with effectiveness based on pooled treatment effect from 8 trials in this patient population

	Risk group 1	**Risk group 2**	**Risk group 3**	**Risk group 4a**	**Risk group 4b**
Odds ratio index hospitalisation with early intervention	1.42	1.42	1.42	1.42	1.42
Hazard ratio in follow-up period with early intervention	0.69	0.69	0.69	0.69	0.69
Incremental cost (£)	4 819	4 852	5 788	6 163	6 129
Incremental QALY	0.0824	0.1847	0.2397	0.4517	0.4178
ICER (£)	58 490	26 265	24 143	13 646	14 673

The results of the interaction model, which allowed the treatment effect to vary with the baseline risk in RITA 3, showed that higher risk was associated with a decreasing odds ratio of a composite endpoint during the index hospitalisation. Furthermore, a more pronounced positive treatment effect was seen in patients with high risk in the follow-up period. Consequently, the cost-effectiveness in patients at high risk was somewhat improved compared to the base-case scenario of a common treatment effect. Conversely, for patients at low risk, cost-effectiveness was much less favourable comparing with the base-case scenario (Table 8).

Table 8. Cost-effectiveness results with effectiveness permitted to vary according to baseline risk in RITA 3

	Risk group 1	**Risk group 2**	**Risk group 3**	**Risk group 4a**	**Risk group 4b**
Odds ratio index hospitalisation with early intervention	1.71	1.67	1.67	1.56	1.47
Hazard ratio in follow-up period with early intervention	0.86	0.80	0.72	0.62	0.50
Incremental cost (£)	4 746	4 774	5 574	6 552	7 214
Incremental QALY	-0.0185	0.0952	0.1876	0.5507	0.6886
ICER (£)	Dominated	50 131	29 711	11 898	10 476

Other sensitivity scenarios indicated that the base-case results appeared robust to the assumptions required for the long-term extrapolation with the exception of the duration of the treatment effect of an early interventional strategy after the 5 years of trial follow-up (Table 9). Extending the duration of the treatment effect beyond the 5 years observed in RITA 3 had an expected positive effect on cost-effectiveness, hence an early interventional strategy could be considered cost-effective in more patients under such scenarios.

Table 9. Cost-effectiveness results when using different assumptions for the duration of treatment effect after the 5-year trial period

Treatment effect scenario	**Risk group**	**Assumption of duration of treatment effect**			
		Base case*	10 years	15 years	lifetime
Constant RITA 3 treatment effect	1	53 760	34 901	27 949	13 920
	2	22 949	15 410	11 652	7 850
	3	21 325	15 754	13 159	10 473
	4a	11 957	9 631	8 446	7 600
	4b	12 750	9 707	8 904	8 270
Interaction between treatment effect and risk at randomisation	1	Dominated	187 947	121 044	45 130
	2	50 131	28 163	21 553	14 354
	3	29 711	19 681	16 218	12 781
	4a	11 898	9 450	8 334	7 600
	4b	10 476	7 934	7 348	6 906

Results presented as cost per QALY gained of early intervention compared with conservative.
*Assumes no continued treatment effect after 5 years of trial follow-up.

In summary, the results show that, in patients presenting with NSTE-ACS at high risk of further cardiac events, an early interventional strategy is associated with a gain in QALYs at an additional cost likely to be considered acceptable when compared with a conservative strategy. However, for patients at low risk, an early interventional strategy is associated with a high cost per QALY gained. For patients at intermediate risk, the cost per QALY gained is within generally accepted thresholds, so decisions about cost-effectiveness are likely to be finely balanced. The extent to which the duration of treatment effect after the 5 years of trial follow-up may change these conclusions will depend upon the strength of the decision makers' beliefs about the duration of the treatment effect, and whether the treatment effect is considered to be constant or is likely to vary across different risk groups.

Endarterectomy in patients with asymptomatic carotid artery stenosis

The results of the cost-effectiveness analysis show that the cost per QALY gained is equal to or less than 500 000 SEK for men aged 73 or younger (Figure 9). The cost per QALY gained was high for women at all ages (1 800 000 SEK for 55-year-olds and 120 000 000 SEK for 84-year-olds, figure not shown). Cost-effectiveness acceptability curves for 4 subgroups are shown in Figure 10.

Figure 9. Incremental cost-effectiveness ratios of CEA compared with BMT for men aged 55 to 84

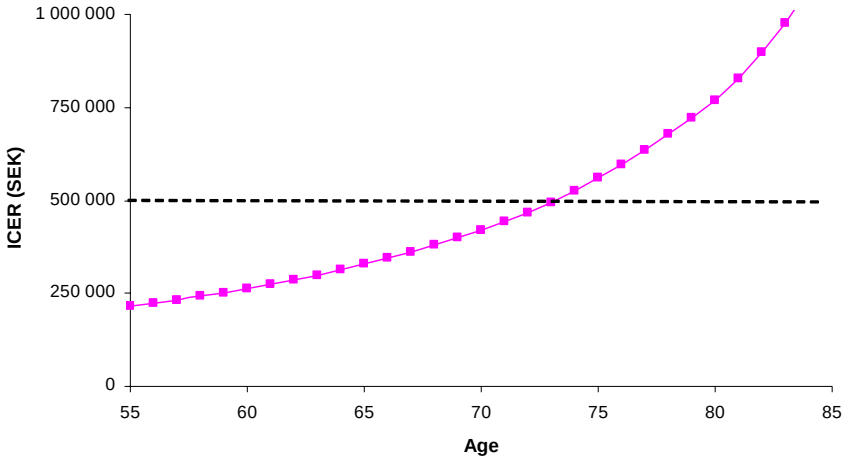
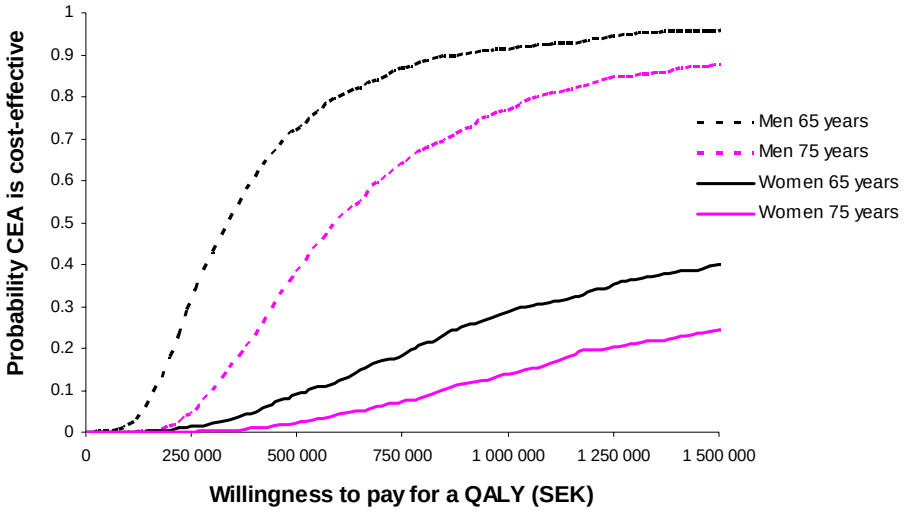


Figure 10. Cost-effectiveness acceptability curves for the CEA strategy



Similar to the case study investigating the cost-effectiveness of an early interventional strategy, the base-case results appear robust to the assumptions required for the long-term extrapolation, with the exception of the duration of the treatment effect of the CEA strategy. Extending the duration of the treatment effect showed that the CEA strategy could be cost-effective in a broader set of patients (Table 10).

Table 10. Cost-effectiveness results when using different assumptions for the duration of treatment effect after the 5-year trial period

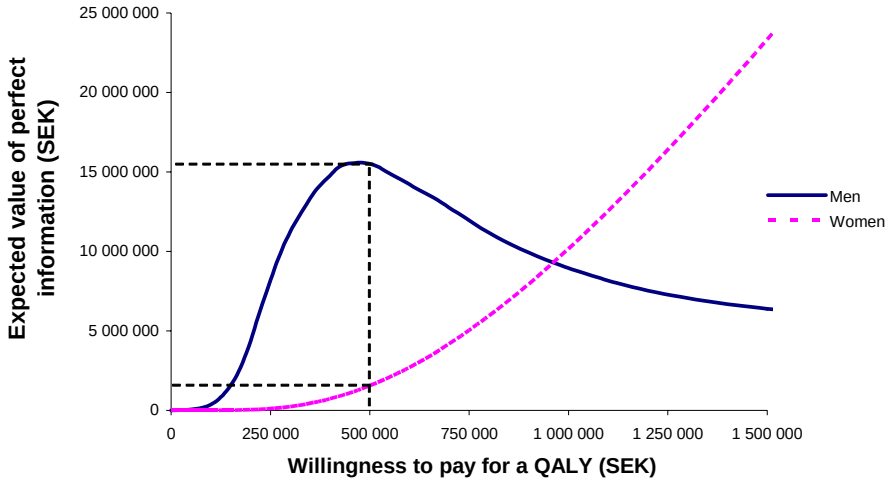
	Assumed duration of treatment effect			
Analysed subgroup	**5 years (base case)**	**10 years (additional 5 years)**	**15 years (additional 10 years)**	**Lifetime**
65-year-old men	328 292	130 602	82 716	58 723
75-year-old men	559 836	298 144	249 995	235 135
65-year-old women	2 955 765	665 837	440 996	334 092
75-year-old women	7 407 869	1 450 603	1 091 892	1 007 945

Results presented as cost per QALY gained of CEA compared with BMT.

Treatment effect refers to the relative risk of non-perioperative stroke of CEA compared with BMT.

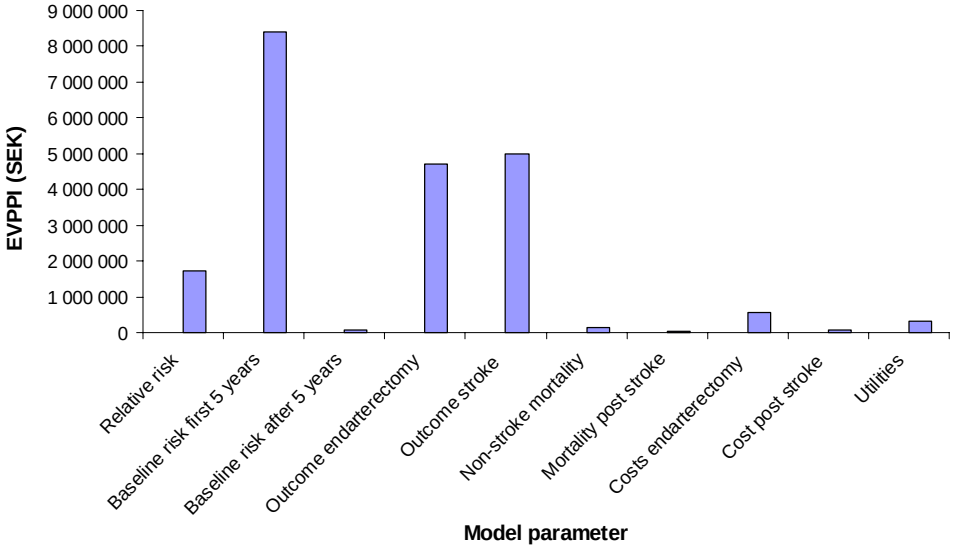
Applying a willingness to pay for a QALY of 500 000 SEK, the total EVPI for the decision to adopt a CEA strategy across all subgroups is about 17 000 000 SEK. The EVPI is substantially higher in men (approximately 15 500 000 SEK) compared with women (1 500 000 SEK). This is mainly due to the fact that the adoption decision is less uncertain in women as the probability of the CEA strategy being cost-effective is low. Furthermore, fewer women are diagnosed with asymptomatic carotid artery stenosis, hence the EVPI per patient is multiplied with a smaller number for women compared with men. Detailed results of all subgroups are available in the appendix. The relationship between willingness to pay and the estimated EVPI is shown in Figure 11 for men and women, respectively.

Figure 11. Expected value of perfect information for the decision to adopt a CEA strategy



The EVPPI is shown in Figure 12 for a willingness to pay for a QALY of 500 000 SEK. The baseline risk of stroke with the BMT strategy is the model parameter associated with the highest EVPPI (approximately 8 400 000 SEK).

Figure 12. Expected value of perfect information for model parameters



Relative risk: relative risk of non-perioperative stroke with the CEA strategy compared with BMT. **Baseline risk**: risk of non-perioperative stroke with the BMT strategy. **Baseline risk +5**: risk of non-perioperative stroke with BMT after year 5. **Outcome of CEA**: perioperative death or stroke (disabling or non disabling**).** **Outcome stroke**: proportion of strokes being fatal, non disabling and disabling**.** **Mort. asympt**: estimated mortality in the population with asymptomatic carotid artery stenosis. **Mort. stroke**: estimated mortality post stroke**.** **Cost CEA**: cost of endarterectomy. **Cost stroke**: costs associated with the post-stroke states in the model. **Utilities**: utilities associated with health states in the model. EVPPI is estimated at a willingness to pay for a QALY of 500 000 SEK.

In summary, the results show that the CEA strategy has incremental cost-effectiveness ratios below conventional values of willingness to pay for a QALY for men aged 73 or younger. If the duration of the risk reduction of non-perioperative stroke associated with the CEA strategy is assumed to be longer than the 5 years of follow-up observed in the ACST trial, the CEA strategy is likely to be cost-effective in a broader set of patients. The results of the value-of-information analysis show that it may be cost-effective to acquire further information, particularly on the baseline risk of non-perioperative stroke, the outcome of endarterectomy and the outcome of stroke.

5. IMPLICATIONS FOR POLICY

This chapter provides a discussion of the results of the case studies and their implications for policy. The results of the case studies are compared with current treatment recommendations and recommendations for further research. Furthermore, the results of the case studies are compared with the utilisation of the investigated treatment strategies in current clinical practice.

Screening for abdominal aortic aneurysm

At the time of the evaluation, no screening programme for abdominal aortic aneurysm existed in Sweden. However, the present study indicates that the investigated screening programme is likely to be cost-effective, suggesting a need for changing clinical practice. Failing to adopt a screening programme implicates that 800 expected QALYs will be forgone in a population of 40 000 men that could be invited to screening each year in Sweden. These QALYs forgone can be valued at a total of €40 000 000, if the willingness to pay for a QALY is €50 000. Taking the cost of the screening programme into account, adopting a screening program would result in an improvement of total net benefit of €32 280 000 for each yearly cohort of 65-year-old men, employing a willingness to pay for a QALY of €50 000.

The recommendations provided by SBU in 2003 stated that any kind of screening programme for abdominal aortic aneurysm that is contemplated in Sweden should fall within the scope of a scientific study that evaluates all potential consequences. This recommendation appeared to be based on the limited evidence regarding cost-effectiveness. However, the present study indicates that screening is likely to be cost-effective when utilising relevant data available at the time of the recommendation by the SBU. The value-of-information analysis showed that further research is unlikely to be worthwhile. In particular, a scientific study that evaluates all potential consequences, as recommended by SBU, appears to be inefficient use of scarce resources. The costs of setting up such a study will most likely be higher than the expected value, in terms of reduced uncertainty, that it may generate. Although the EVPI for the decision to adopt a screening programme in 65-year-old men is low, it should be pointed out that the estimated EVPPI

showed that nearly all the prevailing uncertainty stems from the probability of rupture. Hence, if further research had been deemed cost-effective, the focus should have been on the probability of rupture. This has important implications for prioritising research. The best way of learning more about the probability of rupture is to follow a cohort of men with a diagnosed abdominal aortic aneurysm. Such a study would not require a randomised design and could perhaps be conducted utilising information that has already been collected in routine clinical practice.

Early intervention in acute coronary syndrome

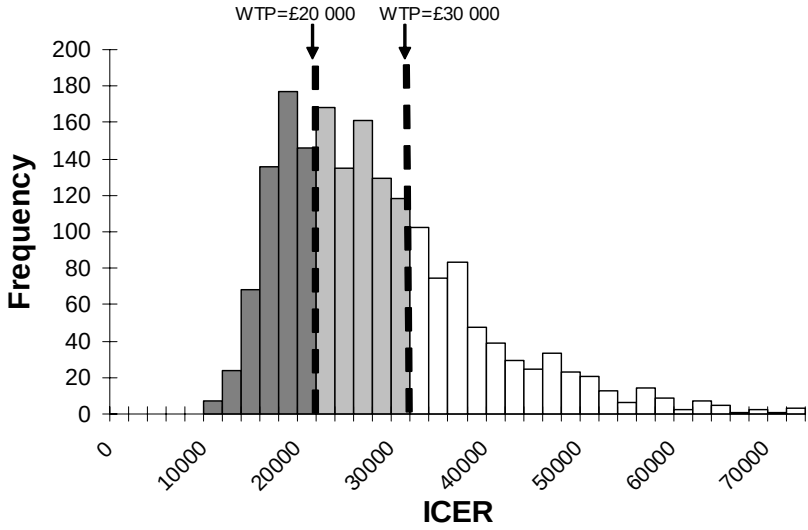
It has not been possible to identify detailed data on the utilisation of an early interventional strategy in the UK at present. Some sources indicate that the use of an early interventional strategy is increasing [66]. Furthermore, no treatment recommendations based on cost-effectiveness or recommendations for further research have been identified.

The results of the present analysis show that an early interventional strategy in patients presenting with NSTE-ACS is likely to be cost-effective in patients at intermediate to high risk of further cardiac events. It has not been possible to compare these results with current clinical practice or recommendations based on cost-effectiveness. However, it should be noted that treatment guidelines based on clinical risk advocate risk stratification in determining the optimal treatment strategy for patients presenting with NSTE-ACS [65]. The results of the present analysis indicate that stratification is also important in guiding decisions based on cost-effectiveness. Assuming that no stratification was carried out, the average ICER of the present analysis would be approximately £22 400. If the willingness to pay for a QALY is £20 000, the early interventional strategy would be deemed cost-ineffective, whereas, at a willingness to pay for a QALY of £30 000, it would be deemed cost-effective.

Such a clear-cut decision will not be efficient. This is illustrated in Figure 13, which reproduces the predicted mean cost-effectiveness for the characteristics of each individual patient in RITA 3. Employing a willingness to pay of £20 000, no patients will be recommended the early interventional strategy, although it is clearly cost-effective in the subset of patients with an ICER below £20 000. These patients are illustrated by the dark shaded bars in Figure 13 and comprise 31 percent of the patients in RITA 3. Employing a willingness

to pay for a QALY of £30 000, all patients will be recommended the early interventional strategy, although it is clearly not cost-effective in the subset of patients with an ICER above £30 000. These patients are illustrated by the white bars in Figure 13 and comprise 30 percent of the patients in RITA 3.

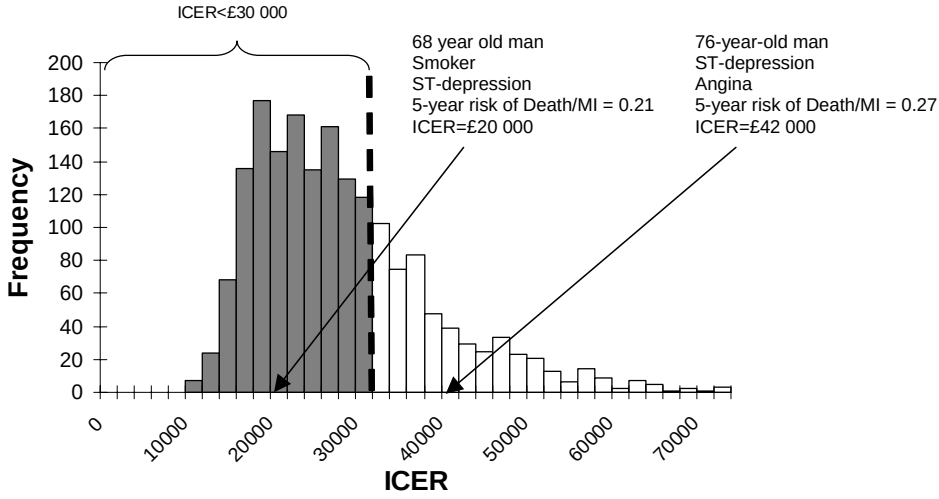
Figure 13. Cost-effectiveness for patients in RITA 3 subdivided by different willingness to pay for a QALY



The example illustrates the importance of stratification when deciding in which patients an early interventional strategy should be deemed cost-effective. In the present analysis it was shown that early intervention is likely to be cost-effective in patients at intermediate to high risk of further cardiac events. However, stratification according to clinical risk is not unambiguous. It was shown in Figure 7 that the 5-year risk of death or myocardial infarction is not always a good predictor of cost-effectiveness. This is further illustrated in Figure 14, where two specified patient characteristics are shown. If willingness to pay for a QALY is £30 000, the early interventional strategy is cost effective for the specified patient characteristics with the lowest risk of death or myocardial infarction. Hence, there is no straightforward way of identifying the particular group of patients with an ICER below the threshold value, i.e., the patients illustrated by the shaded bars in Figure 14. It is necessary to define a specified combination of patient characteristics (of which two are illustrated in Figure 14) and then determine cost-effectiveness for this

particular subgroup. This may be a potential problem when issuing recommendations based on the results of this type of analysis.

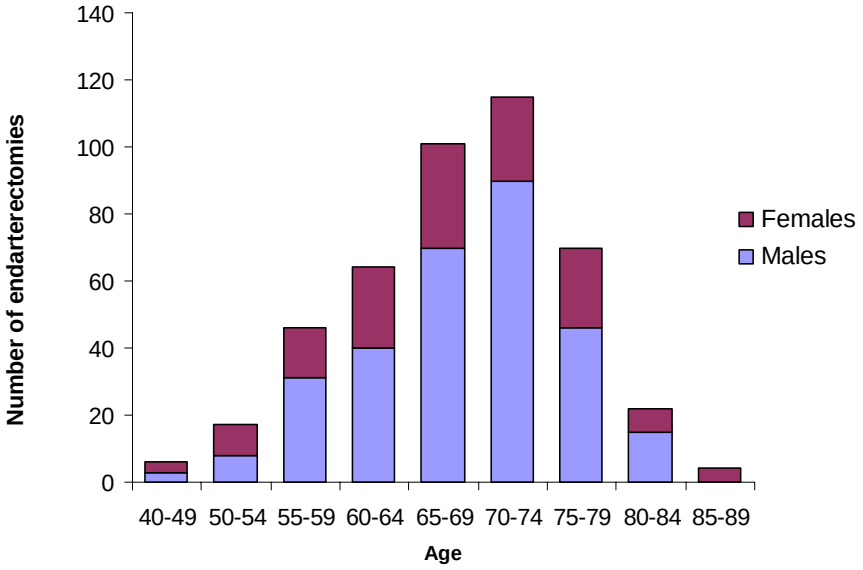
Figure 14. Cost-effectiveness for patients in RITA 3 with details of two specified patient characteristics



Endarterectomy in patients with asymptomatic carotid artery stenosis

Endarterectomy for patients with asymptomatic carotid artery stenosis has been undertaken in Sweden for some time, albeit with great variation in clinical practice. The number of procedures performed in Sweden between January 2004 and March 2006, stratified by age and gender, is shown in Figure 15. The results of the cost-effectiveness analysis showed that carotid endarterectomy can be considered cost-effective in men younger than 73 years of age, but not in women and in men older than 73 years. Comparing the results of the cost-effectiveness analysis with the actual utilisation of carotid endarterectomy shown in Figure 15 reveals that, at present, many patients with asymptomatic carotid artery stenosis are given a treatment that is not cost-effective.

Figure 15. Total number of endarterectomies performed for asymptomatic carotid artery stenosis in Sweden between January 2004 and March 2006



Note that data are from SWEDVASC [72] with details obtained from Claes Forssell, Linköping University Hospital.

It is possible to estimate the expected loss of net benefit resulting from not giving all patients the cost-effective treatment. In this analysis, the total net benefit of giving all patients the treatment strategy with the highest mean net benefit (i.e., the cost-effective strategy) was compared with the total net benefit of providing carotid endarterectomy according to current clinical practice. Hence, in this analysis, the estimated total net benefit of giving all men aged 73 or younger the CEA strategy and all the other patients the BMT strategy is compared with the total net benefit of giving patients the treatment strategies according to current clinical practice as shown in Figure 15. Employing a willingness to pay for a QALY of 500 000 SEK, the gain in net benefit, compared to current practice, of giving all patients the most cost-effective treatment is approximately 6 300 000 SEK for each yearly cohort of patients diagnosed with asymptomatic carotid artery stenosis. Of this improvement, 2 600 000 SEK is in men and 3 700 000 SEK in women. Thus, at present, many patients get a cost-ineffective treatment strategy resulting in a substantial loss of net benefit. It should be noted that extending the duration of the treatment

effect of carotid endarterectomy beyond the 5-year trial follow-up will alter these results.

The treatment recommendations regarding carotid endarterectomy were not very comprehensive. The priority given to carotid endarterectomy for patients with an asymptomatic lesion in the ranking of stroke-related interventions (a "6" on a scale of 1 to 9, where "1" indicates the highest priority and "9" the lowest) is somewhat difficult to interpret. If the ranking of carotid endarterectomy refers to a clear-cut decision of adopting carotid endarterectomy or not, across all patients, the low ranking may be justified as carotid endarterectomy is not cost-effective in women and in men over the age of 73. In fact, a weighted average ICER across all subgroups is approximately 602 000 SEK, leading to the conclusion that carotid endarterectomy is not cost-effective using a willingness to pay for a QALY of 500 000 SEK. However, similar to the findings in the case study on early intervention in acute coronary syndrome, the results of the present analysis clearly show the limitation of such clear-cut decisions. Preferably, the guidelines ought to rank carotid endarterectomy differently depending on the subgroup under consideration.

No guidelines regarding further research into the cost-effectiveness of carotid endarterectomy in patients with an asymptomatic lesion has been identified. The results of the value-of-information analysis showed that it may be cost-effective to acquire further information, particularly on the baseline risk of non-perioperative stroke. When considering further data collection of the parameters with the highest EVPPI, it should be noted that a long-term follow-up of the ACST trial is due to report in a few years time. This report will provide data of up to 10 years follow-up, almost doubling the data currently available for baseline risk of non-perioperative stroke. Furthermore, this follow-up will provide data on the outcome of stroke and the relative risk of non-perioperative stroke.

Designing, and initiating, new studies before the decision-analytic model is updated with this information is unlikely to be cost-effective as the follow-up from the ACST trial will provide substantial information on most of the parameters identified as potentially worthwhile to investigate further. This leads to the conclusion that, at present, men aged around 73 years or younger should be recommended CEA, whereas other patients should be recommended BMT. These recommendations should be revised when the decision-analytic model has been updated with data from the long-term

follow-up of ACST. If there is still substantial value in doing further research after the decision-analytic model has been updated with this information, issues concerning efficient research design can be investigated (an example is available in the appendix).

6. IMPLICATIONS FOR METHODOLOGY

Many issues concerning methodological aspects of using the analytic framework are illustrated and discussed in the previous chapters. It was shown in the case study on screening for abdominal aortic aneurysm that the decision problem could be comprehensively investigated despite the lack of primary studies of a programme comprised of inviting men for a single screening at the age of 65. The importance of estimating cost-effectiveness for different subgroups, or accounting for heterogeneity, was illustrated in the case studies on early intervention in acute coronary syndrome and carotid endarterectomy. Furthermore, the importance of explicitly considering the value of information when issuing recommendations for further research was illustrated in the case studies on screening for abdominal aortic aneurysm and carotid endarterectomy.

In an overall assessment, it could be argued that the case studies themselves provide some evidence that conducting economic evaluations using the proposed analytic framework is feasible. However, some further methodological issues related to the analytic framework are discussed in this chapter.

Event-based modelling - bridging the gap between trials and decision-analytic models?

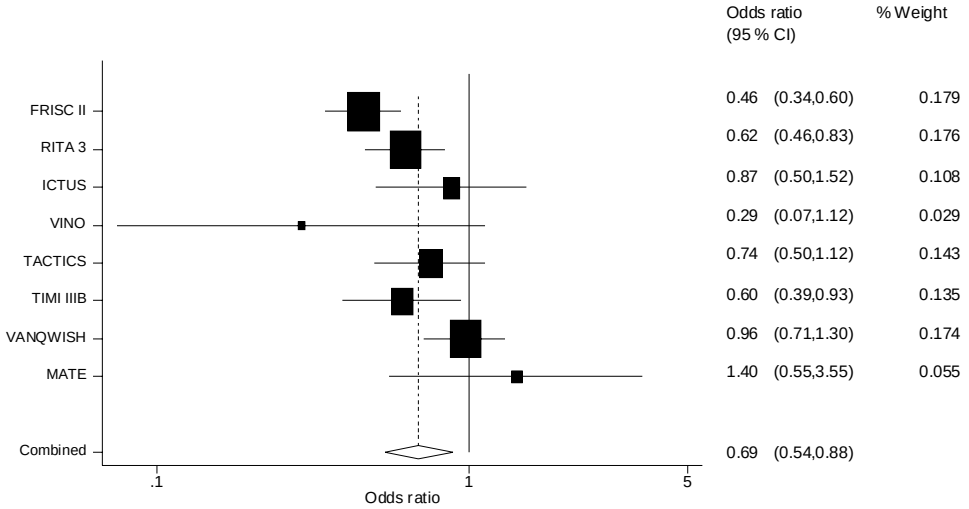
Clinical trials have often been used as a vehicle for economic evaluation, where health outcomes and costs are measured directly on patients participating in the trial. Based on the sample of patients in the trial, a trial-based estimate of cost-effectiveness is established [74]. Advantages of this approach to cost-effectiveness analysis are the high internal validity of the data generated from clinical trials and the fact that trials themselves are well established and understood as vehicles for generating knowledge about uncertain parameters. However, it has been argued that decision-analytic models are often required for the economic evaluation of health care, and, indeed, should be used as a vehicle for economic evaluation rather than clinical trials [29]. Event-based models are emerging as a bridge between the

two approaches where the focus is on primary events observed in a clinical trial and the analysis generally stays close to the trial, and, at the same time, utilises some of the advantages with the decision-analytic modelling approach [37].

The fact that costs and health outcomes often need to be estimated over a lifetime time horizon emphasizes the importance of extrapolation of trial data. The case study on early intervention in acute coronary syndrome used a Markov model to extrapolate survival, costs and QALYs conditional on predicted events from the RITA 3 trial. By extrapolating the results of the parametric survival model employed to estimate cardiovascular death or myocardial infarction, transition probabilities for the Markov model could be estimated beyond 5 years (which was the duration of the RITA 3 trial). In a similar way, costs and QALYs were extrapolated from the equations based on trial data by employing certain assumptions. Hence, the decision-analytic model provides a structure to extrapolate event rates, costs and QALYs, conditional on events having occurred in the trial or not, whereas the statistical equations based on data from the trial provide the data for this extrapolation.

Another example of the bridging between trials and decision-analytic modelling concerns evidence external to a trial. In line with evidence-based medicine [75], it is often argued that economic evaluations should take into account all relevant evidence. In RITA 3, the impact on the results of including evidence from all randomised trials investigating the relative treatment effect of an early interventional strategy was examined. A meta-analysis was performed in order to estimate a pooled treatment effect and the results of this analysis are shown in Figure 16.

Figure 16. Pooled treatment effect on cardiovascular death or myocardial infarction with early interventional compared with conservative strategy



Note: the treatment effect refers to the period between discharge from hospital and end of trial follow-up.

The estimated pooled odds ratio was then used in the parametric survival model rather than the trial based odds ratio. The underlying assumption of this analysis is that the baseline risk is specific for the setting of the study, and can be further controlled for by using covariates in the statistical model, whereas the pooled treatment effect is independent of the baseline risk. This analysis stays close to the original trial data, and, at the same time utilise the advantage of decision-analytic modelling of enabling external evidence to be incorporated into the analysis.

Scenario analyses

All case studies utilise scenario analyses in addition to probabilistic sensitivity analyses. The general aim of running alternative scenarios is to investigate whether altering the value of a parameter has a major effect on the results of the cost-effectiveness analysis. There are different reasons for performing such scenario analysis. In some cases, parameters may differ for different decision makers. Examples include the rate to discount costs and health outcomes, and unit costs to value resource use. In other cases, parameter

values are varied in alternative scenarios due to the fact that they are genuinely uncertain and therefore represent different takes on the evidence. The most obvious example in the present work is the duration of the treatment effect in the case studies of carotid endarterectomy and early intervention in acute coronary syndrome.

The former approach to scenario analyses is not a great concern. The results of the alternative scenarios merely represent the results for different decision makers and can be interpreted accordingly. In the latter approach, however, there is more concern regarding the interpretation of the results. In the case studies using different scenarios for the duration of the treatment effect, it was well illustrated how cost-effectiveness varies with different assumptions regarding the duration. Nevertheless, it should be recognised that such an alteration in the cost-effectiveness results also influences the probability of making the wrong decision and the estimated EVPI. Therefore, it is unclear how the duration of the treatment effect would impact the EVPI, and indeed what the EVPPI for this parameter is. Preferably, this uncertain parameter should have been assigned a probability distribution and formally incorporated into the analysis. This can be achieved using recently developed methods to elicit probability distributions from experts [76]. These methods are under development and rarely seen in present applications, but are likely to provide an improvement in future applications.

Heterogeneity and value of information

The case study on carotid endarterectomy illustrates how detailed analyses of cost-effectiveness in different subgroups may increase the computational burden of the value-of-information analysis. Although this was not clearly seen in the summary results presented in chapter 4, the comprehensive results reported in the appendix provide some evidence for this. This is further highlighted by the simple example of EVSI presented in the appendix, where the simulations are even more time consuming. The computational burden of performing some of these analyses is a limitation at present. This is particularly true for simulations aiming to establish efficient research design. However, it should also be pointed out that the example of EVSI illuminates important aspects regarding efficient research design that are unlikely to be considered at all without the formal approach of value-of-information analysis.

A rational framework for decision-making

The example of heterogeneity and value of information illustrates an important point concerning the analytic framework applied in this thesis. The evaluations tend to become very comprehensive, both in scope and complexity. Comprehensive data collection and more sophisticated methods will improve our ability to provide accurate estimates of relevant parameters. However, it is important to remember that comprehensive economic evaluations are not an aim per se. In fact, the analytic framework implies that the level of comprehensiveness required for the analysis is an empirical question. In some cases, a simple evaluation may prove enough to reach a decision based on cost-effectiveness and to provide a clear indication of whether additional research is required. In other cases, a simple evaluation may reveal that further, and more comprehensive, analyses are required.

In this context, the analytic framework applied in this thesis should be seen as a way of thinking rather than a set of complex methods. It offers a structural approach to inform decision-making where judgements need to be taken what constitutes relevant evidence and treatment options. Based on these judgements it is possible to establish the most cost-effective treatment option given current evidence, whether more information is required and the type of evidence that may be valuable. This approach to decision-making, especially when considering the decision to acquire more information, may offer an improvement to informal approaches, which can often lead to conclusions that 'more research is needed', without any consideration given to the marginal costs and marginal benefits of acquiring more information [77].

Hence, it could be argued that the analytic framework offers a rational approach of asking the right questions. The nature of the decision problem, and, indeed, the resources available to inform the decision problem will be important when determining the appropriate level of analytical complexity. In this context we should always seek to be roughly right rather than precisely wrong, but it may also be more efficient to be roughly right than completely right.

7. CONCLUSIONS

A screening programme for abdominal aortic aneurysm in 65-year-old men is likely to be cost-effective in a Swedish setting from a societal perspective and there appears to be little value in performing further research into this decision problem.

An early interventional strategy in non-ST-elevation acute coronary syndrome is cost-effective in patients at intermediate to high risk of further cardiac events from the perspective of the National Health Services in a UK setting.

Endarterectomy in patients with asymptomatic carotid artery stenosis appears to be cost-effective in a Swedish setting from a societal perspective in men around 73 years of age or younger. It may be worthwhile to conduct further research into this decision problem, although the present analysis should be updated with long-term results from the ACST trial before further research is initiated.

Comparing the results of the present analyses with current clinical practice shows a need for changing clinical practice in Sweden regarding screening for abdominal aortic aneurysm and endarterectomy in patients with asymptomatic carotid artery stenosis. Furthermore, employing the analytic framework applied in the case studies can improve treatment guidelines and recommendations for further research. In particular, treatment guidelines ought to consider in which particular subgroups of patients an intervention is cost-effective.

The case studies indicate that it is feasible to apply the analytic framework for economic evaluation of health care. Methodological development can improve the accuracy with which cost-effectiveness and value of information is estimated, but may also lead to comprehensive and complex evaluations. The nature of the decision problem should determine the level of comprehensiveness required for a particular evaluation.

APPENDIX
DETAILS OF THE CASE STUDIES

This appendix provides some further details of the case studies that are not reported in the accompanying papers.

Screening for abdominal aortic aneurysm

The model structure is described in Paper I, but a more comprehensive outline is given below. Furthermore, data collection and incorporation of data into the model is described in detail below.

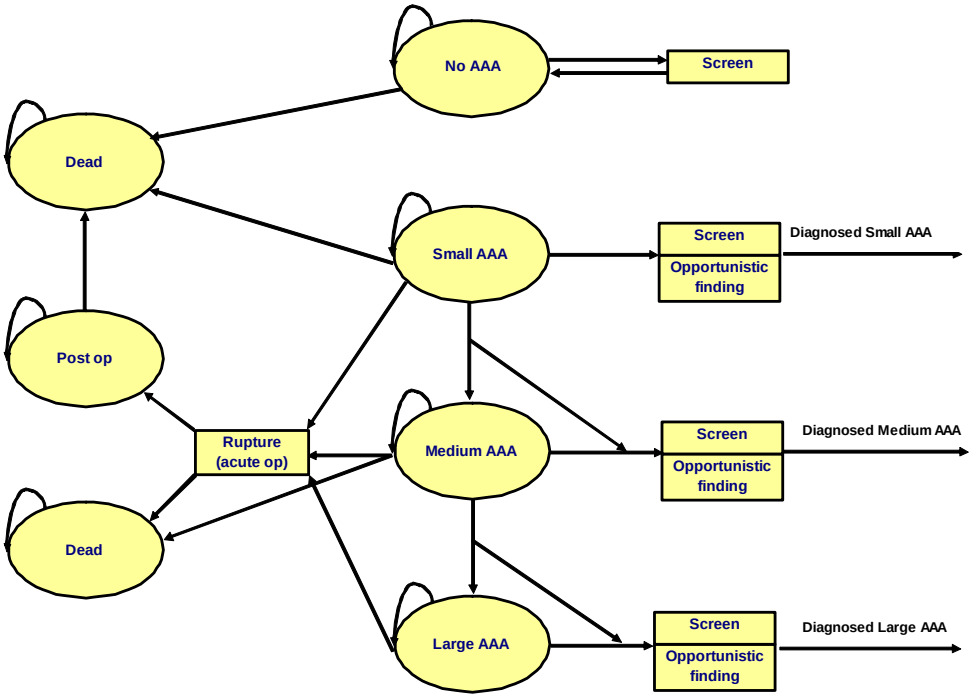
Assumptions and illustration of the model structure

In effect, the model is made up of two parts as an individual can be either undiagnosed or diagnosed. The model structures for the undiagnosed and diagnosed individuals are shown in Figures A1 and A2, respectively. The circles represent health states and the arrows show possible transitions between health states during a Markov cycle. The squares represent events that can occur during a Markov cycle leading to a transition from one health state to another.

At the start of the analysis no individual is diagnosed with an AAA and the cohort is distributed over the No AAA state, and the three AAA states in the undiagnosed part of the model, according to prevalence estimates. A simplifying assumption in the model was that an individual without an AAA at the age of 65 will not develop an AAA later in life [59,78].

Each AAA state is associated with a probability of rupture. Survival after rupture is determined by the probability of reaching hospital and getting an acute operation, and the probability of surviving the operation. Survivors of an acute operation will make a transition to the Post op state. If an AAA grows into a larger size group during a cycle, the individual will make a transition to the next AAA state (from Small to Medium or from Medium to Large AAA). During each cycle there is also a risk of dying from causes not related to AAA and thus make a transition to the Dead state.

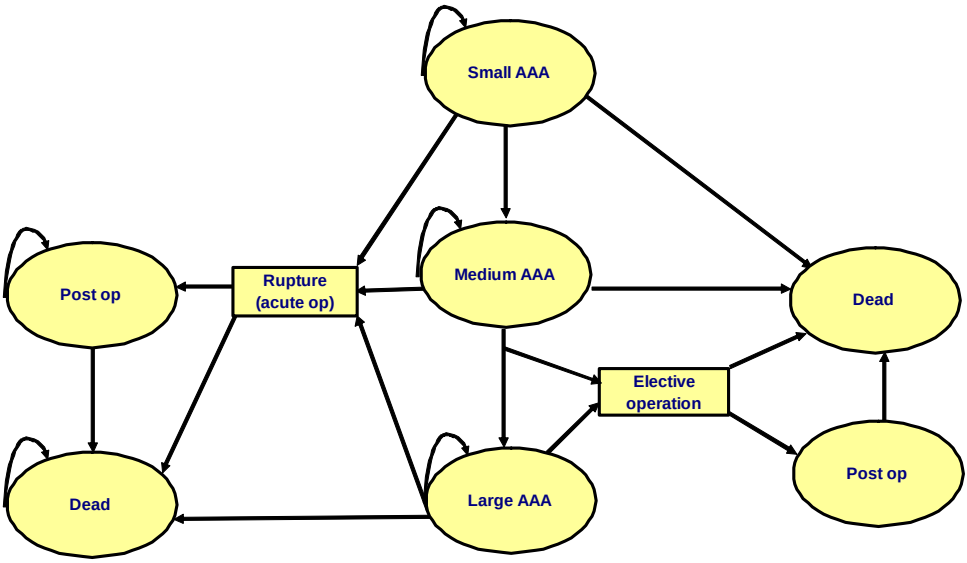
Figure A1. Model structure for undiagnosed individuals



Both the screening strategy and the no-screening strategy allow individuals to be diagnosed opportunistically in each cycle. In addition, with the screening strategy individuals are diagnosed with help of the ultrasound investigation during the first Markov cycle, if complying with the invitation to the screening programme. Sensitivity and specificity of the ultrasound investigation were assumed to be 100 percent. Few studies have investigated the test characteristics of an ultrasound investigation for AAA but some evidence indicate that these are valid assumptions [79]. The assumption of 100 percent sensitivity is investigated in a sensitivity analysis. Individuals diagnosed (opportunistically or by screening) with an AAA > 5.5 cm, fit to undergo, and not declining surgery, are operated electively. Individuals surviving the elective operation make the transition to the Post op state. When diagnosed, individuals are kept under surveillance with regular ultrasound investigations (Small AAA once a year and Medium AAA twice a year). Individuals with a Large AAA that for some reason do not undergo an operation are kept under continuing surveillance by ultrasound twice a year, and they also face a yearly

probability of undergoing an elective operation in subsequent Markov cycles. A 100 percent compliance with surveillance was assumed.

Figure A2. Model structure for diagnosed individuals



Data

Prevalence

Prevalence data was obtained from published screening studies. The identified studies are presented in Table A1.

Random effect meta-analyses were performed on the log-odds of prevalence. Including all identified studies and all studies including only men aged 65 or above yielded similar results. Including the two studies with data on 65-year-olds only, produced a lower prevalence estimate [55,80]. The results from the analyses are summarised in Table A2 and in Figure A3 (references of the studies shown in Figure A3 are available in Table A1).

Table A1. Summary of identified studies reporting the prevalence of AAA

Study	Age		Country	Invited	Number investigated (%)	Number of AAA ≥ 3.0 cm (%)	Year of scan
	Range	Mean					
Ashton [51]	65-74	69	England	33 839	27 147 (80.2)	1 333 (4.91)	1997-1999
Lindholt [54]	65-73	67.5	Denmark	6 339	4 843 (76.4)	191 (3.94)	1994-1998
Scott [55]	65-80	NA	England	3 205	2 342 (73.1)	178 (7.60)	1989-NA
Scott [55]	65		England	210	169 (80.5)	10 (5.90)	1989-NA
Lederle [81]*	50-79	66	US	NA	126 196	5 283 (4.19)	1992-1997
Wilmink [82]	60-69	NA	England	NA	3 107	158 (5.09)	1991-1996
Vazquez [80]	65		Belgium	NA	465	21 (4.52)	1995-1996
Lucarotti [83]**	65		England	2 291	1 748 (76.3)	26 (1.49)	1990-1991
Smith [84]	65-75	NA	England	3 500	2 597 (74.2)	219 (8.43)	1989-NA
O'Kelly [85]**	65		England	NA	118	1 (0.85)	1987-NA
Simoni [86]	65-75	69	Italy	NA	741	65 (8.77)	1991-1994
Boll [87]	60-80	NA	Holland	2 914	2 416 (82.9)	196 (8.11)	NA
Holdsworth [88]	65-79	NA	England	800	628 (78.5)	42 (6.69)	NA
Bengtsson [89,90]	74	74	Sweden	499	375 (75.2)	31 (8.27)	1988
Norman [56]	65-83	73	Australia	17 516	12 203 (63.1)	875 (7.17)	1988-2001

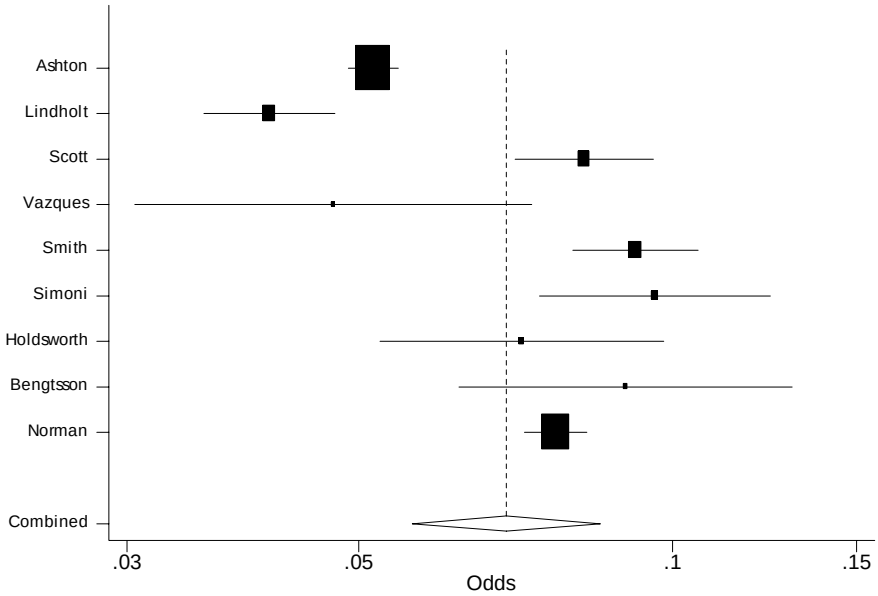
NA: information not available.
* 97 % males in the study population.
** AAA > 40 cm used as definition of AAA.

Table A2. Results of meta-analyses of prevalence (AAA ≥ 3 cm)

Studies included	Pooled estimates*	95 % confidence interval		Number of studies	Estimated prevalence
All	-2.714	-2.900	-2.527	12	6.20%
Including 65-year-olds or older	-2.670	-2.806	-2.731	9	6.50%
Including 65-year-olds-only	-2.960	-3.321	-2.599	2	4.90%

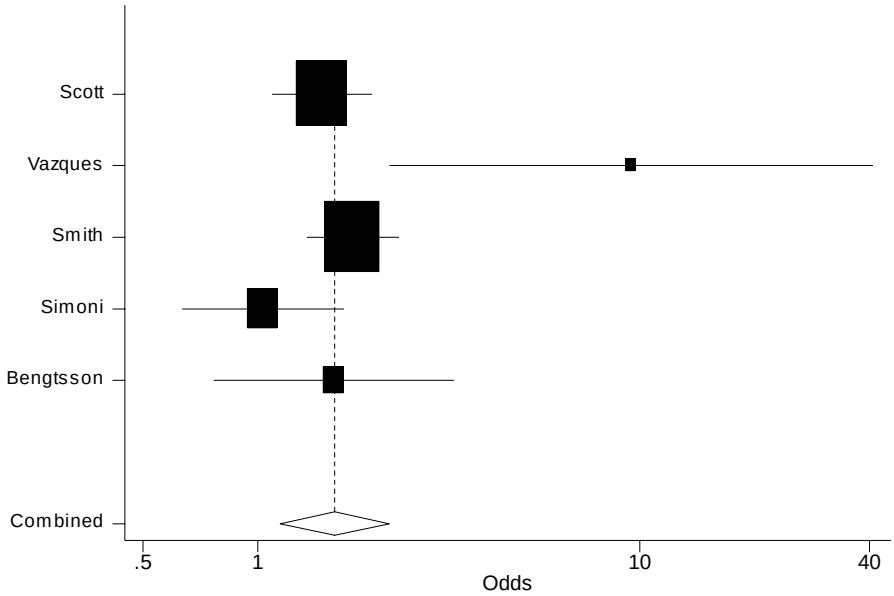
*Log odds of prevalence.

Figure A3. Forest plot of meta-analysis of studies reporting prevalence in men aged 65 years or older



In order not to overestimate the positive effects of a screening programme we used the estimate from the two studies including 65-year-olds only [55,80]. Converting the log-odds yielded a point estimate for the prevalence of 4.9 percent. For the probabilistic analysis, a normal distribution was assumed on the log-odds scale employing the standard error from the meta-analysis. Five studies reported the proportion of total AAAs in the interval $3 \leq AAA \leq 4$. The result of the meta-analysis is shown in Figure A4. The point estimate of log-odds was 0.463 with a 95 percent confidence interval of 0.134 - 0.792 corresponding to an estimate for the proportion of AAAs being small of 0.614. As for total prevalence, a normal distribution was assumed on the log-odds for the probabilistic analysis employing the standard error from the meta-analysis. The conditional probability of an AAA being medium, given that it is not small, was estimated in a similar way employing the two studies reporting this data [80,89]. The point estimate for the log-odds was 0.287 with a 95 percent confidence interval of -0.773 - 1.348, yeilding a point estimate for this conditional probability of 0.571.

Figure A4. Results of meta-analysis on the proportion of total AAAs being small



Summarising the point estimates of prevalence used in the model show a total prevalence of 4.9 percent for 65-year-old men. The estimated proportion of AAAs in different size groups was 0.614, 0.220, and 0.166 for small, medium, and large AAAs, respectively.

Operative mortality

Mortality directly associated with elective and acute operations was estimated using data from the Swedish Vascular Registry (SWEDVASC) [91]. In SWEDVASC, vascular procedures and the outcomes of these procedures are registered [91]. In recent years, nearly 90 percent of all operations for AAA have been reported to the registry. Data from 1987 to 2001 was employed in this study. During this period of time data from 2 562 and 3 364 acute and elective operations, respectively, were available for men 65 years old or above. Deaths occurring within 6 months of an operation were defined as operative mortality. To estimate the probability of death, logistic regressions were fitted to the data using age-group dummies. The predicted log-odds and corresponding standard errors from the regressions are shown in Table A3 for different age groups, together with the estimated probabilities of operative mortality. For the probabilistic analysis, the uncertainty in the predicted

probabilities was characterised using a normal distribution on the log-odds predictions employing the standard errors presented in Table A3.

Table A3. Mortality within 6 months of elective and acute surgery

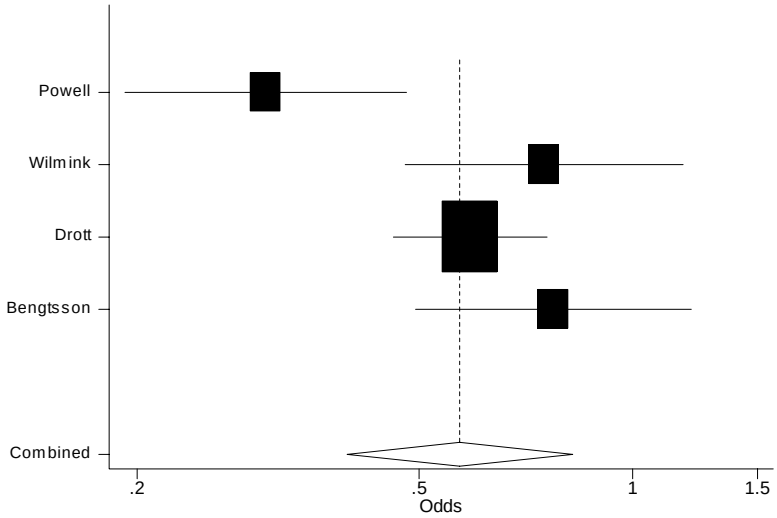
Age	Number of observations	Predicted mean log-odds	Predicted standard error	Probability
Elective operation				
65-69	852	-2.9346	0.1565	0.0505
70-74	1243	-2.6902	0.1163	0.0636
75-79	962	-2.1541	0.1056	0.1040
> 79	307	-1.9875	0.1753	0.1205
Acute operation				
65-69	553	-1.2939	0.1035	0.2152
70-74	819	-0.5745	0.0728	0.3602
75-79	689	-0.2010	0.0766	0.4499
> 79	501	0.1239	0.0895	0.5309

Predicted log-odds and standard errors are from the logistic regression.

Probability of being operated when rupture

Evidence suggests that the proportion of individuals with a ruptured AAA reaching hospital and undergoing an operation has increased over time [92]. The log-odds of a random effects meta-analysis on the four recent studies identified [49,82,92,93] was -0.561 with a standard error of 0.187, corresponding to a probability of 0.36. The results are shown in Figure A5. For the probabilistic analysis, the uncertainty in the estimated probability was characterised using a normal distribution on the log-odds employing the standard error from the random effects meta-analysis.

Figure A5. Forest plot of meta-analysis of the proportion of patients undergoing an acute operation when suffering AAA rupture



Postoperative survival prognosis and mortality not related to AAA

Postoperative survival prognosis was estimated employing data from SWEDVASC [91]. In the dataset from SWEDVASC, long-term postoperative survival after an operation was available. As described above, deaths within 6 months of an operation were defined as operative mortality. Thus, the long-term survival prognosis included individuals alive 6 months after operation. Survival status for these individuals was available in the dataset until December 31 2000. As type of operation was not a good predictor of long term survival once the first 6 months after operation had been removed data from both types of operation was used in the analysis. A time-to-event Weibull model was estimated including age as a covariate. The results are shown in Table A4.

Table A4. Results from the time-to-event Weibull regression model on long-term survival post surgery (log scale)

Variable	Coefficient	Standard error
Age	0.0533	0.0034
Constant*	-7.4914	0.2542
LnGamma**	0.4711	0.0180

*Constant is the hazard at time zero.

**Shape parameter where a value less than (above) 0 on the log scale indicates a decreasing (increasing) hazard over time.

The age coefficient was updated with the age of 65 in the regression equation to derive the estimated hazard function, which was then used to estimate yearly probabilities of death. The estimated yearly probabilities of death were higher than standard mortality for individuals less than 90 years old. When an individual turned 90 years old in the model, standard mortality was higher than the estimated AAA mortality and therefore, the estimates from the Weibull model were no longer used and standard mortality was employed instead. Uncertainty in the mortality estimates was incorporated by defining distributions for the parameters of the Weibull regression. Multivariate normality on the log scale was assumed employing the standard errors of the regression coefficients. Cholesky decomposition was employed to preserve the correlation between regression parameters.

For men without an AAA, age-specific standard mortality rates were used [94]. The standard mortality rates were defined as deterministic in the model. Considering that the survival prognosis of AAA individuals is worse than that of the normal population, mortality unrelated to the AAA for individuals with an untreated AAA was estimated by using the long-term survival prognosis of operated individuals described above. The long-term survival prognosis after an operation was assumed to reflect the general health status of patients with an AAA, with respect to death due to other causes, as their probability of having further problems related to their operated aneurysm is very small [95,96]. This assumption was investigated in a sensitivity analysis where all individuals with an AAA that had not been operated were given standard mortality instead. In Table A5, the yearly age-specific standard mortality probabilities and the yearly mortality probabilities estimated from the Weibull regression are shown for individuals aged 65 to 75. It can be seen from the table that, for instance, an individual aged 67 years in the model (i.e. in Markov cycle 3) face a probability of death from other causes of 0.018 if free from an AAA and a probability of death from other causes of 0.048 if operated (and surviving) in any of the previous cycles or if having a not yet operated AAA.

Table A5. Yearly probabilities of death in the model

Age	Standard mortality	Post op*/AAA-mortality**
65	0.015	0.018
66	0.017	0.036
67	0.018	0.048
68	0.021	0.059
69	0.023	0.068
70	0.025	0.077
71	0.028	0.084
72	0.032	0.092
73	0.034	0.099
74	0.038	0.104
75	0.043	0.111

*Post op: mortality in the postoperative state.
**AAA mortality: mortality with a not yet operated AAA.

Probability of rupture

In a Medline search (the most recent search was performed in July 2004) the search terms 'abdominal aortic aneurysm' was combined with 'risk of rupture' and 'natural history'. This search generated over 800 references of which most were not relevant. Investigating headings and abstracts, seven studies were identified as potentially useful. Due to large differences in study design and reporting of results it was not possible to combine the studies in a formal meta-analysis.

Small AAA

Several studies indicated that the yearly probability of rupture of a small AAA was less than 0.01 [48,97-99]. In one study it was estimated that 1 of 184 small AAAs would rupture in one year giving a point estimate of 0.0054 for the probability of rupture [99]. A beta distribution, Beta(1, 183), was defined for this parameter.

Medium AAA

In two large randomised trials a yearly probability of rupture of a medium AAA was 0.006-0.01 [100,101]. Other studies have reported similar findings [48,99,102]. As for small AAAs, one study estimated the number of AAAs that would rupture in a defined population, suggesting that 1 out of 63 medium AAAs would rupture in a year giving a point estimate of 0.015 [99]. A beta distribution, Beta(1, 62), was defined for this parameter.

Large AAA

Several studies indicated that the yearly probability of rupture of a large AAA was about 0.15 [97,102-104]. One study reported the number of patients with a large AAA that ruptured in one year (5 of 32), giving a point estimate of 0.156 for this probability [102]. A beta distribution, Beta(5, 27), was defined for this parameter.

Growth of AAA

In a Medline search (the most recent search was performed in July 2004) the search term *abdominal aortic aneurysm* was combined with *growth rate* and *natural history.* This search generated some 250 references. Investigating headings and abstracts, twenty references were identified as potentially useful. As for the studies identified investigating rupture probabilities, differences in study design and reporting of results precluded a formal meta-analysis.

From small to medium AAA

Several studies investigating growth of small AAAs were identified [105-110]. In most studies the average growth, measured as mm per year, was reported. However, there are some difficulties with the incorporation of this type of data into the model as the parameter of interest is the probability of moving from the Small AAA to the Medium AAA health state. Collin et al. reported that 16 of 52 patients with a small AAA had an AAA that was larger than 4 cm at 3 years follow-up [107]. The estimated three-year probability of a transition from the Small to Medium AAA state was thus 0.308, corresponding to a yearly probability of 0.115. A similar finding was reported by Santilli et al [108]. A beta distribution for the three-year probability, Beta(16, 36), was defined for this parameter.

From medium to large AAAs

From two large clinical trials, the proportion of individuals with a medium AAA growing larger than 5.5 cm was around 50 percent in 4 years follow-up [100,101]. An estimated four-year probability of making a transition from Medium AAA to Large AAA was thus 0.50, yielding a yearly probability of making the transition of 0.159. A beta distribution, Beta(283, 283) was defined for the four-year probability reflecting the number of individuals in one of the trials.

Proportion complying with invitation

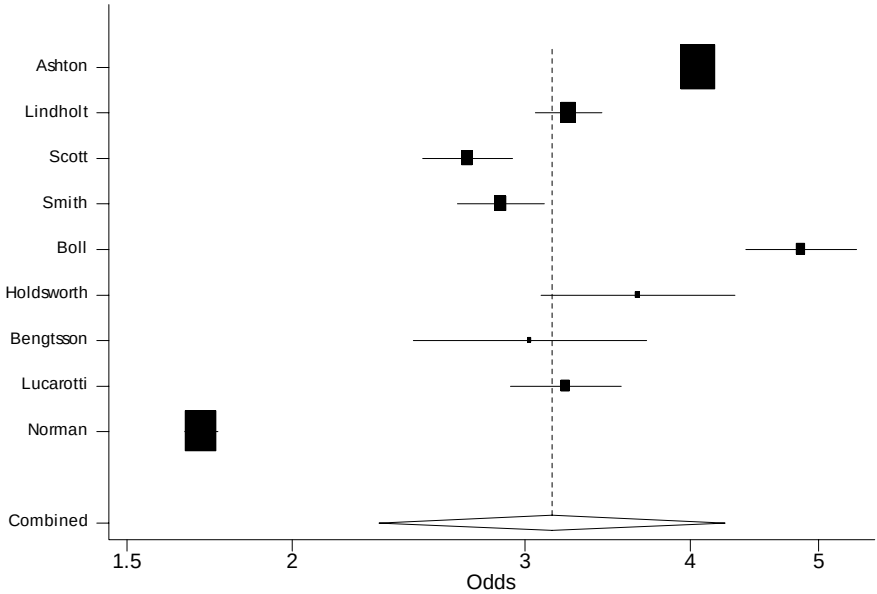
Most evidence indicated that the proportion of individuals complying with the invitation was 70-80 percent (see Table A1). The results of a random effect meta-analysis of all studies identified reporting compliance are shown in Table A6 and Figure A6. In Table A6, the results are also shown when pooling the results from the two studies reporting compliance for 65-year-olds only [55,83]. The point estimates are very similar when including all studies (0.765) or only the two reporting compliance for 65-year-olds only (0.773). The estimate using the two studies reporting compliance for 65-year-olds was used in the model. For the probabilistic analysis the uncertainty in the estimated proportion was characterised using a normal distribution on the log-odds employing the standard error from the random effects meta-analysis.

Table A6. Results of random effect meta-analysis of studies reporting compliance with the invitation

Studies included	Pooled estimates*	95 % confidence interval	Number of studies	Estimated compliance
All	1.178	1.000-1.376	9	0.765
Including 65-year-olds only	1.236	1.021-1.452	2	0.773

*Log-odds of compliance.

Figure A6. Forest plot of meta-analysis of the proportion complying with the invitation to screening



Proportion electively operated

The estimated proportion of individuals actually undergoing an operation when candidates for elective surgery (a detected large AAA) was 84 percent [55]. A beta distribution, Beta(31, 6), was defined for this parameter. No study was identified where the probability of undergoing an elective operation at a later stage was reported. Built on expert opinion it was estimated that 1 of 6 individuals would be operated yearly despite not being operated on diagnosis of an AAA > 5.5 cm. A beta distribution, Beta(1, 5) was defined for this parameter.

Opportunistic case-finding

No studies investigating opportunistic case-finding were identified. We performed a small registry study in the county of Östergötland, Sweden, in order to investigate the yearly probability of being opportunistically detected with an AAA. Protocols of performed investigations at the department of radiology, the Vrinnevi Hospital, Norrköping, were searched for abdominal aortic aneurysm. In these protocols, all AAAs detected during a defined period of one year would be registered. In total, 9 new cases of AAAs were reported for men aged 65-69. Applying the estimated prevalence of 4.9 percent on the population in the catchment area of the Vrinnevi Hospital the total number of AAAs in this population could be defined. In total 3572 men aged 65 to 69 years lived in the catchment area indicating 175 expected AAAs in this population. Nine of these 175 were detected during one year leading to a yearly probability of being detected opportunistically of 0.051. For the probabilistic analysis the number of detected cases was held constant and prevalence varied.

Sensitivity

Some evidence indicate that the assumption of 100 percent sensitivity of an ultrasound investigation seems plausible. However, there is little information available on this parameter and in a sensitivity analysis a scenario was run using 80 percent sensitivity and a beta distribution, Beta(50, 13), was defined for this parameter.

Costs

Costs of acute and elective operations are allocated to the cycle in which they occur. Costs for the invitation and the administration of the screening programme arise in the first cycle of the model in the screening strategy. The costs of ultrasound investigations, both the initial and the surveillance

investigations, are allocated to the cycles when they occur. Taking a societal perspective all relevant costs should in principle be included. Loss of production due to absence from work is normally an important cost item when a societal perspective is taken. As all individuals in the study are 65 years of age we have, however, assumed that everyone is retired and hence this cost was not included. A private travel cost, incurred when attending the ultrasound investigation, was included. A much debated cost item in economic evaluations is the cost of added life years and this cost was considered in an alternative scenario [111].

Costing studies were undertaken in order to estimate costs for the invitation, ultrasound investigation, and operations. Secondary sources were employed to get estimates of private costs associated with an ultrasound investigation and costs of added life years.

Invitation to screening

All individuals in the screening strategy will get an invitation to the ultrasound investigation. The calculated cost of the invitation, including the cost of administrating the screening programme was €6.67. Based on one administrative assistant working 1 day a week during a year, the cost of staff was €5.11 per invitation (assuming gross earnings of €2 000 a month). The remaining €1.56 included office space, postage and stationary. The cost of the invitation was not varied in the probabilistic analysis.

Ultrasound investigation

The calculated cost of an ultrasound investigation was €42.78. Wages for a biomedical analyst and an assistant nurse were included in this cost. It was assumed that it would take 100 days to screen all men complying with the invitation. The wages for a biomedical analyst and assistant nurse were available from Statistics Sweden. The total estimated costs per ultrasound investigation attributed to wages were €15.67 and €14.11 for a biomedical assistant and assistant nurse, respectively.

As the screening is performed in a primary care setting with mobile equipment a transport cost for staff was included in the calculations. It was assumed that staff needs to travel 100 kilometres per day at a cost of €0.11 per kilometre. A fixed cost of €3 333 per year for a car was also allocated to the cost of the ultrasound investigation.

An annual cost of the ultrasound equipment was calculated assuming it could be used for 5 years with an acquisition cost of €38 889. A laptop with an acquisition cost of €3 333, assuming it could be used for 3 years was also included in the cost of the ultrasound investigation.

The cost of office space needed to carry out the investigations was calculated using unit costs of €1.11/m^2 per day. It was assumed that a room of 10 m^2 would be needed to carry out the ultrasound investigations. The cost calculations for the ultrasound investigation are shown in Table A7. As for the cost of invitation, the cost of an ultrasound investigation was not varied in the probabilistic analysis.

Table A7. Calculated cost of an ultrasound investigation (€)

Cost item	Cost/investigation
Wages biomedical analyst	15.67
Wages assistant nurse	14.11
Car	3.67
Ultrasound equipment	7.44
Laptop	1.00
Office space	0.89
Total cost	*42.78*

Surveillance

The cost of an ultrasound investigation calculated above was also used for planned investigations when individuals are under surveillance when detected with an AAA.

Private cost of ultrasound investigation

For individuals attending the ultrasound investigation, time and travel costs are incurred. These costs were investigated in a British study [112]. In this study 499 men aged 65 to 79 years attending a screening programme were included. The average private cost was 4.79 GBP (1994 prices) which is equal to €7.41 inflated to 2003 prices. These results agree with estimates for prostate cancer screening. Carlsson and colleagues estimated a private cost of €7.22 (inflated to 2003 prices) for individuals attending prostate cancer screening [113]. A private cost of €7.41 was used in the model.

Operations

The calculations of the total costs for operations are based on a fixed and a variable cost. The fixed cost is by definition the same for every operation. Variable costs are time in operation theatre, use of blood products, and bed-days postoperatively. For variable costs, a unit cost is established and then multiplied by actual resource use for each operation. Information on unit costs and resource use was primarily taken from Linköping University Hospital.

Fixed costs were categorised into preoperative assessment, disposables, equipments and others. In the costs for preoperative assessment, it was assumed that two thirds of acutely operated individuals have an acute ultrasound investigation and one third has a CT. The use of disposables does not differ between acute and elective operations. Regarding the cost of ambulance, it was assumed that patients travel on average 30 kilometres to a hospital that performs acute operations. A unit cost of €6.67 per kilometre was used for the ambulance cost. As 50 percent of the acute operations are performed on non-office hours an added cost for staff to actually get to the hospital was added.

The calculated total fixed costs were €2 751 and €1 653 for acute and elective operations, respectively. A summary of the calculations of fixed costs is shown in Table A8.

Table A8. Fixed costs of acute and elective operations (€)

Cost item	Acute operation	Elective operation
Preoperative investigations		
Doctors visit		151
CT	102	306
Electrocardiogram		22
Ultrasound (acute)	74	
Disposables		
Anaesthesia	198	198
Operation*	480	480
Instruments		
Cell saver	202	202
Operation**	48	48
Sterilization	30	30
Heating	126	126
Other		
Pharmaceuticals	91	91
Ambulance	400	
Staff	1000	
Total fixed costs	*2751*	*1653*

*Including an aortic graft.

The variable costs consist of time in theatre, bed-days, and blood products. Resource use is measured in physical units and assigned probability distributions for the probabilistic analysis. Unit costs are not associated with sampling uncertainty and are therefore not varied in the probabilistic analysis. The estimation of unit costs is presented first followed by the assessment of actual resource use.

The main component in the cost per minute in theatre is the cost of staff. It was assumed that on average, 2 nurses and 2 surgeons are present at both acute and elective operations. Furthermore, it was assumed that on average 1.5 anaesthetists and 1.5 anaesthetist nurses are present at an acute operation. For an elective operation, it was assumed that 1 anaesthetist and 2 anaesthetist nurses are present. According to the financial department at the Heart Centre, Linköping University Hospital, the cost per minute for a nurse is €1.11 and the cost per minute for a surgeon/anaesthetist is €2.22. Furthermore, the cost of an operating theatre was estimated at €55.56 per hour (€0.93 per minute). Fifty percent of the acute operations are performed during non-office hours at a 100

percent higher cost. This was incorporated in the estimates by making all costs for staff 50 percent higher. This should not be confused with the extra cost included in the fixed costs above. The added fixed cost represents the cost to actually get the staff to the operation room. Once at the operating room the staff cost more on non-office hours which was included in the cost per minute.

The estimated cost per minute was €18.44 and €12.04 acute and elective operations, respectively. A summary of the calculations of cost per minute is shown in Table A9.

Table A9. Cost per minute for acute and elective operations (€)

Cost item	Acute operation	Elective operation
Number of nurses (operation)	2	2
Number of nurses (anaesthesia)	1.5	2
Cost per minute (nurses)	1.67	1.11
Total cost per minute (nurses)	*5.85*	*4.44*
Number of surgeons	2	2
Number of anaesthetists	1.5	1
Cost per minute (surgeon/anaesthetists)	3.33	2.22
Total cost per minute (surgeon/anaesthetists)	*11.66*	*6.67*
Cost per minute operation room	*0.93*	*0.93*
Total cost per minute	*18.44*	*12.04*

The unit cost per bed-day and blood products are shown in Table A10. The cost per bed-day is from the Department of Vascular Surgery, Linköping University Hospital. The cost per bed-day at the intensive care unit (ICU) has been estimated by the financial department of Linköping University Hospital. The unit cost of blood is from the Department of Laboratory Medicine, Linköping University Hospital.

Table A10. Cost per bed-day and blood products (€)

Cost item	Unit cost
Bed-day (Department of Vascular Surgery)	494
Bed-day (ICU)	2 222
Blood (ml)	0.41

In order to calculate costs per operation, recourse use for variable cost items need to be quantified. Data on time in the operating department for acute and elective operations was obtained from an internal registry for quality control from the Department of Vascular Surgery, Linköping University Hospital. In total, data was available from 22 acute and 41 elective operations (including operations from January 2002 to February 2004). The mean time in the operation department was 270 minutes and 324 minutes for an acute and elective operation, respectively. As the time in operation theatre is associated with sampling uncertainty it was defined with a probability distribution for the probabilistic analysis. A gamma distribution was used for this purpose [28]. From the sample of acute and elective operations, mean and standard errors for the number of minutes needed for each operation were calculated. Gamma distributions were defined for these parameters using methods-of-moment fitting [28]. Gamma(202, 1,3) and Gamma(363, 0,9), for acute and elective operations, respectively.

The amount of blood used was estimated from the same sample of operations. The mean blood use for an acute operation was 2 865 ml and a gamma distribution was defined for this parameter in the same way as described above for minutes in the operation department (Gamma(12, 245)). Corresponding figures for an elective operation was 1 606 ml (Gamma(21, 76)).

Data on the number of bed-days at the vascular surgery department was obtained from SWEDVASC, where the total numbers of bed-days are registered, including time in the ICU [91]. Information on the time spent in the ICU was available from the Swedish intensive care registry (SIR). The time spent in the ICU was subtracted from the total number of bed-days according to SWEDVASC in order to calculate the number of bed-days exclusive of time spent in the ICU. Mean bed-days, according to SWEDVASC, was 14.9 and 12.2 days for acute and elective operations, respectively. Corresponding time in the ICU, according to SIR, was 6.5 days and 3.2 days, respectively. In order to incorporate uncertainty in the estimates of these parameters, gamma distributions were defined for the total number of bed-days, Gamma(222, 0,07) for an acute operation, and Gamma(304, 0,05) for an elective operation. It was assumed that the proportion between bed-days in the ICU and bed-days in the surgery department is the same in every simulation in the probabilistic analysis. Hence, in each simulation. the total numbers of bed-days are drawn for both types of operation. The time spent in the ICU is then calculated from

that value using a constant percentage (43.6 percent and 26.2 percent for acute and elective operations, respectively).

A summary of the cost calculations is shown in Table A11.

Table A11. Total costs of acute and elective operations

Cost item	Acute	Elective
Fixed cost	*2 751*	*1 653*
Unit cost per minute	18.44	12.04
Time per operation (minutes)	270	324
Total cost time in operation room	*4 979*	*3 901*
Unit cost bed days	494	494
Number of bed days	8.4	9
Total costs bed-days	*4 150*	*4 446*
Unit cost ICU	2 222	2 222
Number of days ICU	6.5	3.2
Total cost ICU	*14 443*	*7 110.4*
Unit cost blood (ml)	0.41	0.41
Blood use (ml)	2865	1606
Total cost blood	*1 175*	*659*
Total cost operation	*27 497*	*17 769*

Note that the costs in Table A11 are point estimates. When analysing the model, a value is drawn from the defined distributions representing actual resource use. The total costs for an operation is calculated by applying the unit costs on resource use and, hence, a new cost for respective operation is generated in each simulation of the probabilistic analysis.

Costs of added life years

Previous estimates of these costs are shown in Table A12 [114]. Gamma distributions were defined for the probabilistic analysis. Employing the assumed standard errors shown in Table A12 gamma distributions could be defined for these parameters.

Table A12. Costs of added life years

Cost item	Mean cost	Standard error	Distribution
Yearly cost of added life years (65-74 year olds)	19 219	2 222	Gamma(75, 257)
Yearly cost of added life years (75-84 year olds)	22 043	2 778	Gamma(63, 350)
Yearly cost of added life years (≥85 year olds)	31 422	4 444	Gamma(50, 629)

QALYs

Potential gains in life-expectancy from a screening programme are realised late in life when the health status of individuals often is poorer than for younger people. Using age adjusted quality-adjustment weights from a normal population incorporates this aspect into the analysis. QALY-weights, and the defined distributions used in the model are shown in Table A13 [115].

Table A13. QALY-weights for males in the normal population

Age	QALY-weight	Standard error	Distribution
60-69	0.83	0.012	Beta(812, 166)
70-79	0.81	0.018	Beta(384, 90)
80-88	0.74	0.037	Beta(103, 36)

No long-term effect on quality of life after a diagnosis of AAA has been demonstrated and was therefore not incorporated in the base case analysis [51,116]. In a sensitivity scenario, individuals diagnosed with an AAA were assigned a decrement in quality of life of 0.071, corresponding to moving from no problem to some problem on the anxiety question in the quality of life instrument Euroqol EQ-5D [117]. For the probabilistic analysis, a gamma distribution was defined for this parameter, Gamma(12.6, 0.01). Furthermore, no long-term negative effects on quality of life have been demonstrated in individuals surviving an acute or elective operation and hence no quality adjustment of the Post op state was included in the base case analysis [118-126]. In a sensitivity scenario, individuals in the Post op state were assigned a utility decrement of 0.1. A gamma distribution was defined for this parameter, Gamma(16, 0.01).

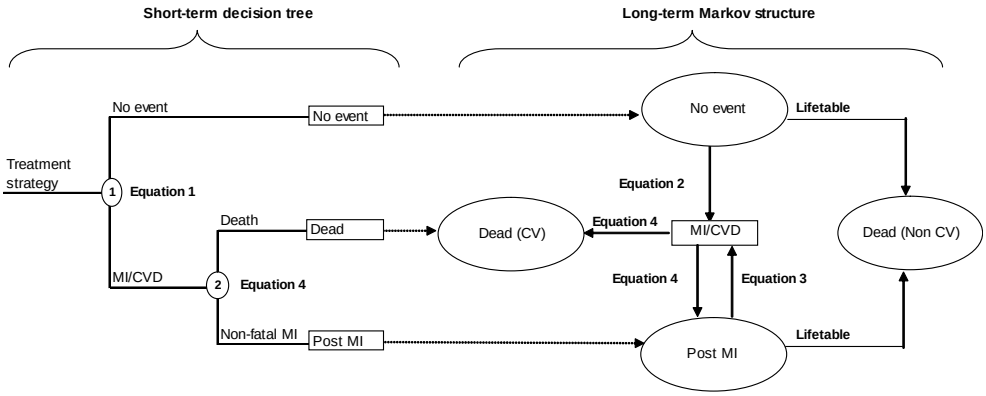
Early intervention in acute coronary syndrome

This section describes the model structure as this is not presented in detail in Paper III. Furthermore, details of the statistical analyses and how the results of these analyses were incorporated in the decision-analytic model are provided. Finally, some results of the analyses performed to validate the model are provided.

Model structure

A series of statistical models (referred to as equations) were estimated to determine the rates of cardiovascular death or non-fatal myocardial infarction (MI) during the index hospitalisation and the remainder of the trial follow-up period. These estimates of effectiveness were then incorporated into the cost-effectiveness model which is based on a short-term decision tree and a long-term Markov structure as shown in Figure A7. The short and long-term models represent the index hospitalisation and the post-index hospitalisation respectively. Costs and QALYs were determined for the index hospitalisation and for each state in the long-term Markov structure.

Figure A7. Model structure



MI: myocardial infarction. CV: cardiovascular. CVD: cardiovascular death.

In the short-term decision tree, patients face a risk of the combined endpoint of cardiovascular death or MI as shown by the chance node labelled "1". A conditional probability determines if that endpoint is fatal or not, illustrated by the chance node labelled "2". Thus, three mutually exclusive outcomes were considered in the short-term tree (as indicated by the boxes in Figure

A7): non-fatal myocardial infarction; cardiovascular death; and no event. These outcomes also represent health states in the long-term Markov structure described below. The probabilities of the different endpoints during the index hospitalisation are used to estimate the proportion of patients starting in each of the health states in the long-term model.

Logistic regression models (Equation 1 and 4 in Figure A7) were used to estimate the probabilities associated with each chance node. The regression models are presented in the data section below. Each outcome in the tree is associated with a cost, including the cost of treatment. The mean time of the index hospitalisation was 7.2 days in RITA 3 and for 90 percent of the patients the index hospitalisation was 13 days or shorter. To simplify the modelling exercise, the short-term tree was assumed to be instantaneous in time. Hence, the main purpose of the short-term tree was to distribute the analysed cohort over the starting states in the long-term Markov structure and to estimate the short-term costs associated with each treatment strategy.

The Markov structure was made up of three states: No event; Post MI; and Dead, each represented by an oval in Figure A7. Note that two separate Dead states are drawn in Figure A7, representing death due to cardiovascular and non-cardiovascular causes. Yearly Markov cycles were implemented. It should be noted that if the acute phase of the disease had been included in the Markov structure, monthly cycles would probably have been required. However, since the acute phase of the disease is modelled in the short-term decision tree, yearly cycles were considered appropriate to model disease progression in the long-term.

As noted previously, the proportion starting in each state is determined by the outcome of the short-term decision tree. The majority of the patients in each treatment strategy will start the long-term model in the No event state, although the proportion of individuals starting in this state will differ between the investigated strategies depending on their relative effectiveness during the index hospitalisation. Each year, individuals in the No event state face a probability of a composite endpoint of non-fatal MI or cardiovascular death (CVD), which is estimated using a Weibull proportional hazards model (Equation 2 in Figure A7). Note that the box (MI/CVD) in Figure A7 indicates that a composite event has occurred during a cycle and does not represent a formal health state since patients are then assigned to either a fatal or non-fatal state based on a separate calculation. As the individual-patient data indicated

a decreasing risk of a composite endpoint with respect to time from the index hospitalisation, this transition probability was made time dependent in the model. In a similar manner to the approach applied in the short-term decision tree, a conditional probability was then assigned to reflect the chance that this endpoint was fatal or not (Equation 4 in Figure A7). Although this probability was estimated from the same statistical model informing the estimate applied in the short-term decision tree, the estimates will not necessarily be the same in the short-term and longer-term models. This issue will be discussed in more detail below.

Patients having a non-fatal myocardial infarction in the model make a transition to the Post MI state. Once in the Post MI state, individuals face a risk of a second composite endpoint (Equation 3 in Figure A7). Analogous to the No event state, a decreasing risk with respect to the time elapsed from the myocardial infarction was employed for this transition. However, a different technical solution was needed in this part of the model since a myocardial infarction can occur in any cycle and therefore precludes using specific cycle numbers to model time dependence. Instead, tunnel states were employed to incorporate time dependence in this probability. Tunnel states are arranged so that they can be visited only in a fixed sequence and therefore make it possible to reduce or increase the risk of a clinical event as the time spent in a health state elapse. For instance, the year immediately after a myocardial infarction (the first year in the Post MI state in the model) is associated with the highest risk of a second composite endpoint. The following four years in the Post MI state are associated with successively lower risks of a second composite endpoint. For simplicity, only one Post MI state was drawn in Figure A7 but this state is effectively 5 states (with each state representing an additional year alive after a myocardial infarction). Provided no second composite endpoint occurs during a cycle, individuals only spend one cycle in each of the first four Post MI states before entering the fifth (last) Post MI state. Once an individual reaches the fifth Post MI state, they stay in that state for the sixth and subsequent cycles (years) after an MI if no second composite endpoint occurs. Hence, time dependency in the probability of a second composite endpoint was incorporated for the first five years after a non-fatal myocardial infarction in the model. Thereafter, the probability of a second composite endpoint is no longer dependent on the time elapsed from the first myocardial infarction. The conditional probability of a second composite endpoint being non fatal was estimated using Equation 4.

Patients suffering cardiovascular death at any time in the model move to the CV dead state. In each cycle patients also face a yearly risk of dying from non-cardiovascular causes. The death states are considered absorbing states in that once patients enter these states subsequent transitions are not allowed.

Data

Analysis of effectiveness

All statistical analyses included previously identified risk factors for cardiac events measured at randomisation and randomised treatment [62]. These risk factors were included as covariates in the statistical models and are shown in Table A14. A stepwise backward selection procedure was employed when estimating the statistical models. With this approach, a model including all specified covariates is estimated first and the most statistically non-significant covariate is then dropped (provided the level of significance of this covariate is higher than the pre-specified level). The model is then re-estimated in an iterative process until only statistically significant variables remain in the model. Within the statistical models, the general statistical approach was to drop non-significant covariates at the 5 percent level. However, covariates of structural importance, such as the treatment covariate in Equation 1 and 2, were considered important to keep in the statistical models regardless of statistical significance.

Table A14. Covariates included in the statistical models

Covariate	Explanation
Age	Discrete indicator for every 10 years over 60 years of age
Diabetes	Indicator of diabetes at study inclusion
Previous MI	Indicator of previous MI at study inclusion
Smoker	Indicator of smoker at study inclusion
Pulse	Discrete indicator for every 5 beats per minute
ST depression	Indicator of ST depression at study inclusion
Angina	Indicator of angina grade 3 or 4 at study inclusion
Male	Indicator of male
Left BBB	Indicator of left bundle branch block at study inclusion
Treat	Indicator of randomised to early interventional strategy

Logistic regression model of risk of cardiovascular death or myocardial infarction during the index hospitalisation (Equation 1)

A logistic regression model was used to estimate the risk of the combined endpoint of cardiovascular death or MI during the index hospitalisation. The

index hospitalisation was defined as the time from randomisation to hospital discharge.

Weibull proportional hazards model of risk of cardiovascular death or myocardial infarction during the remainder of trial (Equation 2)

To estimate the risk of the combined endpoint of cardiovascular death or MI during the remainder of the trial period a time-to-event Weibull proportional hazards model was employed with the starting time set at hospital discharge [127]. In extrapolating beyond the period of trial follow-up (5 years), a conservative assumption of no continued treatment effect from the early interventional strategy was made. Different assumptions concerning the duration of the treatment effect after the 5 years of trial follow-up were investigated in alternative scenarios. Further details of the extrapolation are given below.

Weibull proportional hazards model of risk of a second composite endpoint of cardiovascular death or myocardial infarction (Equation 3)

There were insufficient patients in RITA 3 to estimate the risk of a second composite endpoint of MI or cardiovascular death following a non-fatal MI. Instead, the risks of a first composite endpoint were used, multiplied by the coefficient for the additional proportionate risk for patients who had a non-fatal MI prior to their entry into the RITA 3 trial. The rationale for this approach was that with a previous history of myocardial infarction a first event in the trial in fact represented at least a second event for these patients. No treatment effect of an early interventional strategy was included when estimating this risk which is a conservative assumption with respect to the cost-effectiveness of early intervention.

Logistic regression model of the proportion of composite endpoints being non-fatal (Equation 4)

A logistic regression model was employed to estimate the proportion of composite endpoints being non fatal. A dummy variable was used to investigate if this proportion was different between the index hospitalisation and the remainder of follow-up.

Death from non-cardiovascular causes

As the risk equations estimate the risk of dying from cardiovascular causes, patients' risk of dying from non-cardiovascular causes needs to be included in the analysis. This risk was estimated using UK sex- and age-specific lifetables

adjusted to exclude cardiovascular mortality [128,129]. This approach simplifies extrapolation. Furthermore, using lifetables rather than estimating non-cardiovascular causes from the trial data can be argued to better reflect the risk of non-cardiovascular causes in clinical practice due to selection criteria in the recruitment to RITA 3.

Costs

Comprehensive resource use data were collected in patients in RITA 3 up to one-year follow-up and have been described and analysed in detail elsewhere [64]. Two standard OLS regressions were used to determine mean costs for the alternative strategies during the index hospitalisation and for the remainder of the trial. Mean costs were estimated, differentiating between management strategies, for patients with and without a composite endpoint of cardiovascular death or MI. When extrapolating beyond one year, the analysis assumed no difference between the treatment strategies in the cost of patients not experiencing the composite event.

Health-related quality of life

Health-related quality-of-life (HRQoL) data were collected in patients in RITA 3 at randomisation, 4 months, 1 year, and yearly thereafter. Methods and results have been reported elsewhere [63]. To estimate QALYs for each treatment strategy, quality-adjustment weights (utilities) are required on a scale where 0 represents death and 1 represents full health. These were obtained using the EQ-5D instrument, which was used in the trial, and employing the preferences of the UK general population [117,130]. A standard OLS regression was employed in order to estimate the mean HRQoL of patients with different risk profiles at randomisation. A panel-data approach was then employed in order to estimate changes in HRQoL after randomisation, differentiating between the two management strategies and whether a composite endpoint of cardiovascular death or MI had occurred. For the long-term extrapolation, no difference in HRQoL between the treatment strategies was assumed after the first year in patients not having experienced a composite endpoint. In a similar manner to the approach previously described in relation to Equation 3, this was considered to be a conservative assumption with respect to the cost-effectiveness of early intervention. The long-term decrement in HRQoL in patients who had experienced a non-fatal MI was based on the estimated HRQoL observed during the trial of patients who experienced such an event before or during the trial.

Alternative scenarios

Two alternative scenarios were investigated relating to the estimation of differential effectiveness. Firstly, a pooled treatment effect was estimated from all randomised clinical trials comparing early interventional and conservative strategies in NSTE-ACS [62,131-137]. The rationale for this analysis was that data from RITA 3 could be considered relevant to inform the baseline risk of patients in the UK. However, it could be argued, once controlling for baseline risk, that the treatment effect should be pooled from all randomised trials comparing an early interventional strategy with a conservative strategy in order to incorporate all available evidence in the cost-effectiveness model. Data for this analysis were extracted from an earlier published meta-analysis [61] and updated with the results from the more recent ICTUS trial [134], the long-term results of FRISC II [133] and the present RITA 3 analysis. Data were pooled employing a random-effects model, with the estimate of heterogeneity coming from the inverse-variance fixed-effect method [31]. For the trials not reporting the treatment effect of the composite endpoint of myocardial infarction or cardiovascular death, the reported treatment effect of myocardial infarction or death was used as an approximation. To incorporate the estimates of the treatment effect from the meta-analyses into the cost-effectiveness model, the mean log-odds ratios and standard errors from the meta-analyses were used in equations 1 and 2 instead of the odds/hazard ratios estimated from RITA 3 trial data. In the second alternative scenario, an interaction between treatment effect and risk at randomisation was employed. In this analysis, the statistical models included an interaction between the risk score defined in RITA 3 [62] and treatment effect.

Results

Effectiveness

Logistic regression model of risk of cardiovascular death or myocardial infarction during the index hospitalisation (Equation 1)

Equation 1 shows that increasing age and severe angina (grade 3 or 4) were associated with an increased risk of a composite endpoint during the index hospitalisation (Table A15). Although not statistically significant, the early interventional strategy was associated with an increased risk of a composite endpoint during the index hospitalisation (odds ratio 1.520, 95 percent confidence interval 0.864 - 2.675). The limited number of covariates which were significant in the equation may be due to the relatively small number of composite endpoints occurring during the index hospitalisation.

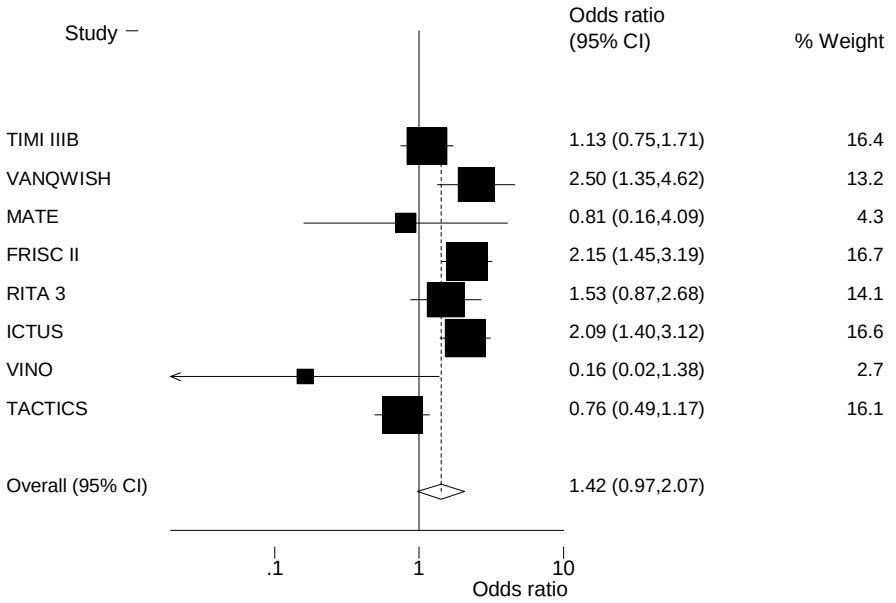
Table A15. Odds ratio of composite endpoint of cardiovascular death or myocardial infarction during the index hospitalisation

Covariate	Odds ratio*	95 % Confidence interval
Treat	1.520	0.864 to 2.675
Age	1.731	1.262 to 2.374
Angina	1.893	1.086 to 3.299
Constant**	0.010	0.005 to 0.019

*Odds ratio > 1 indicates an increased risk of cardiovascular death or myocardial infarction.
**Note that the constant is the odds of an event when no covariate is updated.

As previously mentioned, alternative scenarios for the treatment effect were investigated. The results of pooling the treatment effect of 8 trials are shown in Figure A8. The odds ratio of the pooled treatment effect from the meta-analysis was similar to the odds ratio in RITA 3 (odds ratio 1.42, 95 percent confidence interval 0.97 - 2.07 in the pooled analysis compared to an odds ratio of 1.53, 95 percent confidence interval 0.87 – 2.68 in RITA 3).

Figure A8. Forest plot of meta-analysis of treatment effect in the index hospitalisation



The results of the statistical model including an interaction between baseline risk and treatment effect showed that a higher risk was associated with a decreasing odds ratio of a composite endpoint during the index hospitalisation (Table A16). For example, the odds ratio of a composite endpoint in the early interventional strategy compared with a conservative strategy approaches 1.76 for low risk patients (risk score approaching 0). For high risk patients (risk score approaching 1), the odds ratio tends towards 1.15.

Table A16. Odds ratio of composite endpoint of myocardial infarction or cardiovascular death during the index hospitalisation including an interaction between risk at randomisation and treatment effect

Covariate	Log odds ratio*	95 % Confidence interval
Treat	0.567	-0.490 to 1.624
Risk score	3.638	1.198 to 6.077
Interaction treat and risk score	-0.424	-3.834 to 2.985
Constant*	-4.593	-5.394 to -3.793

*Note that the constant is the log odds of an event when no covariate is updated.

The equations presented above estimate the odds of particular events. It should be noted that the odds of an event is the ratio of two complementary probabilities and therefore does not represent a probability required to populate the cost-effectiveness model. Hence, the estimated odds need to be transformed. To obtain the relevant probabilities (p) from equation 1, the inverse logit transformation was used [138] given by:

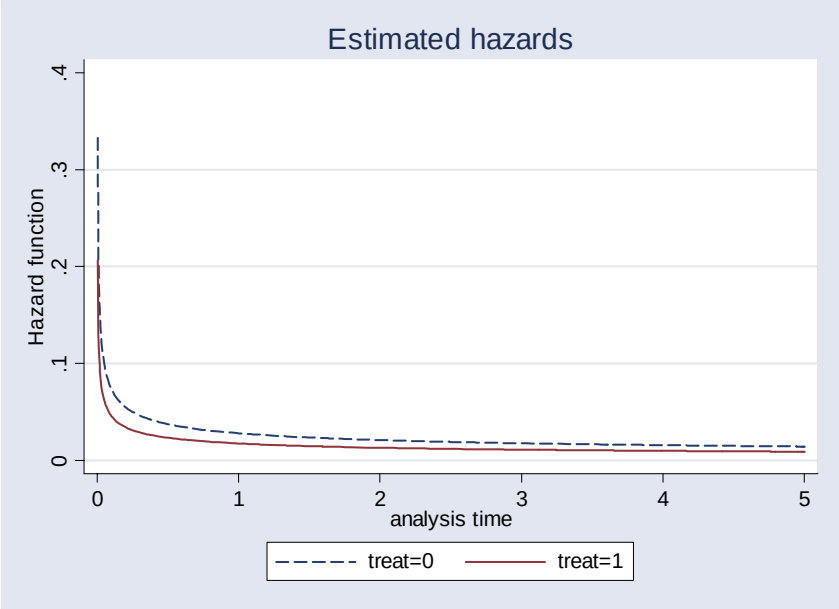
$$p = \frac{e^{X\beta}}{1 + e^{X\beta}}$$

for the covariates, X, and the estimated coefficients on the log scale, β.

Weibull proportional hazards model of risk of cardiovascular death or myocardial infarction during the remainder of trial (Equation 2)

The fact that the shape parameter in the Weibull model is less than 1 indicates that the rate of the composite endpoint of cardiovascular death or MI declines as time elapses from hospital discharge (see Figure A9). This finding is consistent with other studies in this patient group [139].

Figure A9. Estimated hazards of cardiovascular death or myocardial infarction from hospital discharge until end of trial



Treat = 0 is conservative strategy, treat = 1 is early interventional strategy.
Note that the remaining covariates are evaluated at their mean value.

The results of the Weibull model are shown in Table A17. All risk factors but one (angina) were significant at the 5 percent level. However, angina was very close to significance and was kept in the Weibull model as a likelihood ratio test favoured the full model. The early interventional strategy was associated with a statistically significant lower rate of cardiovascular death or MI after the index hospitalisation (hazard ratio 0.621, 95 percent confidence interval 0.464 - 0.830).

Table A17. Hazard ratio of composite endpoint of cardiovascular death or myocardial infarction from hospital discharge until end of trial

Covariate	Hazard ratio*	95 % Confidence interval
Age	1.777	1.499 to 2.108
Diabetes	1.905	1.359 to 2.672
Previous MI	1.471	1.087 to 1.990
Smoker	1.651	1.207 to 2.258
Pulse	1.062	1.012 to 1.114
ST depression	1.423	1.067 to 1.913
Angina	1.323	0.988 to 1.771
Male	1.372	1.007 to 1.869
Left BBB	1.977	1.169 to 3.344
Treat	0.621	0.464 to 0.830
Constant**	0.008	0.005 to 0.015
Ancillary or shape parameter	0.579	0.505 to 0.664

*Hazard ratio > 1 indicate an increased risk of cardiovascular death or myocardial infarction.
**Constant is the hazard at time zero.
***Shape parameter in the Weibull model where a value less than (above) one indicates a decreasing (increasing) hazard over time.

The results of pooling the treatment effect of 8 trials are shown in Figure A10. The pooled treatment effect was similar to the treatment effect observed in RITA 3 (hazard ratio 0.688, 95 percent confidence interval 0.536 – 0.881 compared to an odds ratio of 0.621, 95 percent confidence interval 0.464 – 0.830 in RITA 3).

The results of the statistical model including an interaction between baseline risk and treatment effect are shown in Table A18. Although not statistically significant, the interaction model showed that the positive treatment effect was more pronounced in patients with higher baseline risk. The hazard ratio of a first composite endpoint in the remainder of the trial is close to 1 when the risk score is tending towards 0 and approximately 0.21 when the risk score tends towards 1.

Figure A10. Forest plot of meta-analysis of treatment effect in the follow-up period

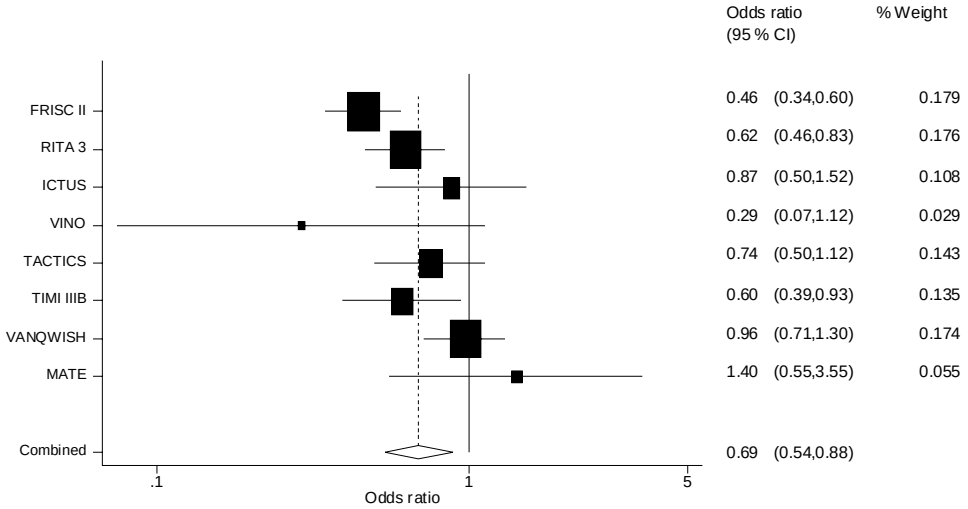


Table A18. Hazard ratio of composite endpoint of cardiovascular death or myocardial infarction from hospital discharge to end of trial including an interaction between risk at randomisation and treatment effect

Covariate	Log hazard ratio*	95 % Confidence interval
Treat	-0.035	-0.581 to 0.511
Risk score	4.925	3.993 to 5.857
Interaction treat and risk score	-1.518	-3.238 to 0.203
Constant*	-3.986	-4.345 to -3.626
Ancillary or shape parameter	-0.545	-0.682 to -0.408

*Note that the constant is the hazard at time 0.

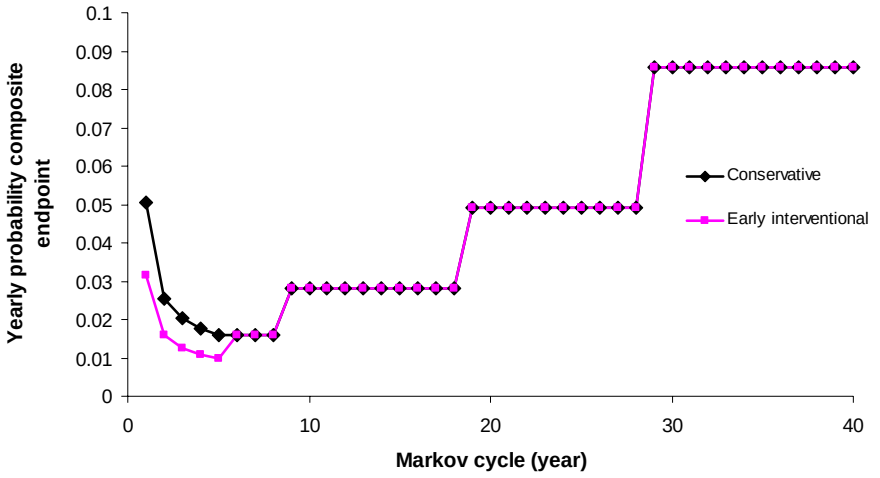
The transition probabilities needed to populate the long-term Markov structure were derived from the results of the statistical models reported above. The yearly transition probability of a composite endpoint in Markov cycle t, tp(t), is given by: $tp(t) = 1 - \exp(\lambda(t-1)^{\gamma} - \lambda t^{\gamma})$. It should be noted that the survivor function of the Weibull distribution is given by: $S(t) = e^{-\lambda t^{\gamma}}$, where $\lambda = X\beta$ for the covariates, X, and the estimated β and γ.

As previously noted, the estimated hazard of a composite endpoint declines relatively rapidly and tends towards a constant hazard after only a few years. Therefore, a declining hazard was used for the first 5 years in the model. Thereafter, a constant hazard, with respect to time after the index hospitalisation, was implemented. This appeared reasonable given the shape of the hazard curve and that follow-up data in RITA 3 was only available for up to 5 years. The estimated hazard for year 5 was thus employed for the sixth and subsequent years in the model.

A complicating issue when estimating the hazard of a first composite endpoint was how to deal with age. The results of Equation 2 indicated a declining hazard that tended towards being constant at 5 years. However, using this constant hazard for the remainder of analysis time failed to incorporate the possible impact of age as patients get older in the model. The dummy variable for age employed in the Weibull model provided a pragmatic approach to take this into account. Every tenth year, the hazard of a composite endpoint was increased by updating the age covariate. We examined the robustness of this assumption in a separate scenario, in which the effect of age on the long-term hazard was excluded. In this scenario, the estimated hazard for the fifth year was not updated with age and a constant risk was thus employed throughout the remainder of the analysis. Furthermore, as noted above, a conservative assumption was made that the treatment effect did not last longer than the 5 years of trial follow-up with different assumptions concerning the duration of the treatment effect after trial follow-up being investigated in alternative scenarios.

The estimated probabilities of a first composite endpoint in the long-term Markov structure are shown in Figure A11 (for a 60-year-old patient setting all other covariates in Equation 2 at the mean value observed in the trial). The assumption of no continued treatment effect after 5 years is clearly seen in the figure as is the effect of employing the variable for age in order to increase the risk of a composite endpoint as patients get older in the model.

Figure A11. Probabilities of a first composite endpoint in the Markov model



Weibull proportional hazards model of risk of a second composite endpoint of cardiovascular death or myocardial infarction (Equation 3)

Equation 2 was used to estimate the risk of a second composite endpoint by updating the covariate for prior myocardial infarction (Table A17). The hazard ratio of this variable indicated that the risk of a second composite endpoint of cardiovascular death or myocardial infarction was estimated to be about 50 percent higher than the risk of a first composite endpoint. Using the results from the Weibull model estimated in equation 2 also imposed a logical time dependency, as patients were getting further away from their MI in the model. Technically this was achieved by employing tunnel states for the first 5 years after a non-fatal myocardial infarction. After 5 years the hazard of year 5 was employed, adjusted for age as patients get older in the model.

Logistic regression model of the proportion of composite endpoints being non-fatal (Equation 4)

All the events reported in the RITA trial (comprising a total of 244 first events and 17 second events) were included in the logistic regression model estimating the probability of a composite endpoint being non-fatal. The results showed that this probability was higher during the index hospitalisation than during the follow-up period (Table A19). This reflects the fact that patients are likely to receive prompt treatment if they experience an MI whilst in hospital. For those patients who had experienced an MI prior to the trial, the composite endpoint was more likely to be fatal. It should be

noted that treatment effect was highly insignificant in this model (odds ratio 1.01, p-value = 0.95). Hence, given that a composite endpoint had occurred, the randomised treatment that patients received provided no additional explanatory power as to whether the composite endpoint was fatal and hence was excluded from the final statistical model.

Table A19. Odds ratio of a composite endpoint being non-fatal

Covariate	Odds ratio*	95 % Confidence interval
Index dummy	3.04	1.614 to 5.726
Age	0.699	0.520 to 0.941
Previous MI	0.492	0.286 to 0.847
Constant**	1.189	0.720 to 1.964

*Odds ratio > 1 indicates an event is more likely to be non fatal.

**The constant is the odds of a composite endpoint being non fatal when no covariate is updated.

Similarly to equation 1, the inverse logit transformation was used to get the estimated probabilities required for the cost-effectiveness model from equation 4 [138].

Death from non-cardiovascular causes

The hazard of dying from non-cardiovascular causes was estimated using general UK population age-and-sex specific lifetables, adjusted to exclude cardiovascular mortality (ICD10 codes I00 to I99) [128,129]. The probabilities are shown in Table A20.

Table A20. Age and sex-specific probabilities of dying from non-cardiovascular causes

Age	Men	Women	Age	Men	Women
45	0.0017	0.0013	74	0.0277	0.0187
46	0.0019	0.0016	75	0.0296	0.0194
47	0.0022	0.0017	76	0.0326	0.0216
48	0.0023	0.0018	77	0.0360	0.0239
49	0.0027	0.0020	78	0.0396	0.0263
50	0.0027	0.0022	79	0.0436	0.0290
51	0.0029	0.0024	80	0.0462	0.0303
52	0.0032	0.0026	81	0.0500	0.0334
53	0.0034	0.0028	82	0.0545	0.0375
54	0.0037	0.0032	83	0.0607	0.0418
55	0.0041	0.0033	84	0.0684	0.0479
56	0.0047	0.0036	85	0.0764	0.0523
57	0.0052	0.0041	86	0.0830	0.0576
58	0.0057	0.0043	87	0.0895	0.0641
59	0.0064	0.0048	88	0.0993	0.0717
60	0.0071	0.0052	89	0.1083	0.0798
61	0.0077	0.0057	90	0.1187	0.0910
62	0.0085	0.0061	91	0.1263	0.1010
63	0.0093	0.0067	92	0.1406	0.1114
64	0.0100	0.0075	93	0.1522	0.1232
65	0.0120	0.0075	94	0.1641	0.1323
66	0.0121	0.0084	95	0.1948	0.1601
67	0.0135	0.0092	96	0.2068	0.1727
68	0.0148	0.0103	97	0.2278	0.1840
69	0.0167	0.0114	98	0.2386	0.1996
70	0.0177	0.0118	99	0.2488	0.2128
71	0.0199	0.0133	100	0.2727	0.2311
72	0.0222	0.0149			
73	0.0246	0.0167			

Costs

During the index hospitalisation, the early interventional strategy was associated with a higher mean cost (mean £5 654, 95 percent confidence interval £5 151 - £6 157) compared with a conservative strategy (Table A21). This additional cost was mainly due to the higher number of angiographies and revascularisations undertaken in the early interventional arm. After controlling for treatment allocation, a non-fatal myocardial infarction or death was associated with additional costs of £6 221 and £7 947, respectively, which included the costs for the administration of thrombolytic drugs, revascularisations and longer hospital stay in wards and intensive care.

Covariates such as age, sex, and ST depression were also associated with higher costs during the index hospitalisation. It should be pointed out that including these covariates in the short-term tree will only influence the absolute cost level in both treatment strategies but have no effect on incremental costs.

Table A21. Estimated costs during the index hospitalisation

Covariate	Coefficient	95 % Confidence interval
MI index	6 221	4 314 to 8 128
Dead index	7 947	5 536 to 10 358
Treat	5 654	5 151 to 6 157
Male	1 035	516 to 1 553
ST depression	1 224	699 to 1 750
Age	878	579 to 1 178
Constant	1 778	1 199 to 2 358

During the first year after the index hospitalisation, the early interventional strategy was associated with a lower mean cost (mean -£1 106, 95 percent confidence interval -£1 562 to -£650) compared with the conservative strategy (Table A22). This reflected the fact that more patients in the conservative strategy had further symptoms that necessitated revascularisation during this period. The results also indicated that patients had a substantially higher mean cost, irrespective of treatment allocation, if they suffered a myocardial infarction within the previous year (mean £5 467, 95 percent confidence interval £3 890 - £7 044) or prior to the trial (mean £724, 95 percent confidence interval £210 - £1 239).

Table A22. Estimated costs after the index hospitalisation

Covariate	Coefficient	95 % Confidence interval
MI year 1	5 467	3 890 to 7 044
Treat	-1 106	-1 562 to -650
Male	586	111 to 1 061
Angina	1 034	550 to 1 518
Previous MI	724	210 to 1 239
Constant	2 735	2 249 to 3 220

Since cost data was only collected for 1-year in RITA 3, certain assumptions were necessary in order to translate the results of the cost analysis into costs associated with the states in the long-term Markov structure. In the cost-effectiveness model, the covariates for sex, angina, and previous MI result in the addition of a constant cost to every state in the model. These covariates are updated as patients progress through the Markov model e.g., the costs for all patients surviving 1 year after an MI have an additional cost of £724 applied for every year they survive without experiencing another event. While the treatment covariate predicts a lower cost for the No event state (£1 106) in the early interventional strategy in the first year, it was unclear whether this differential would continue to exist in the long term. In the absence of longer term cost data we employed a conservative assumption towards the early interventional strategy. After 1 year we assumed that that the rate of revascularisations (the cost item contributing the most to the difference between early interventional and conservative strategy) was the same in the two strategies. Hence, the predicted cost of the early interventional strategy in the first year was applied to both strategies in the second and subsequent years for the No event state.

By updating the 'MI year 1' covariate, a predicted cost for the first year in the Post MI state was obtained. To reflect the higher use of cardiovascular drugs, visits to GPs and hospital admissions assumed to occur during the second and subsequent years after a myocardial infarction, the previous MI covariate was updated. It was assumed that the increased cost of patients having had a previous myocardial infarction would be a good estimate of the long run increase in cost associated with being in the Post MI state. An alternative assumption was considered in a separate scenario, in which no additional costs were applied in the years following a myocardial infarction.

Health-related quality of life

At randomisation, mean HRQoL (in terms of 0 to 1 utilities) were higher for males whereas diabetes, previous myocardial infarction, ST depression and angina were associated with lower HRQoL (Table A23).

Table A23. Estimated baseline utilities

Covariate	Coefficient	95 % Confidence interval
Diabetes	-0.0506	-0.0915 to -0.0096
Previous MI	-0.0443	-0.0761 to -0.0125
ST depression	-0.0660	-0.0950 to -0.0369
Angina	-0.0738	-0.1033 to -0.0443
Male	0.0727	0.0436 to 0.1017
Constant	0.6924	0.6636 to 0.7212

Note that the constant shows the utility at randomisation for a patient without any of the risk factors included in the analyses.
A negative (positive) sign indicates that the risk factor is associated with a lower (higher) utility at randomisation.

Binary covariates were included to represent whether the utility measure was taken at month 4 (D4) or subsequently (D12) and an interaction term for treatment group. The model assumes, for patients who do not experience a myocardial infarction, changes in utility at one year are maintained until the end of the follow up period. Binary covariates were also included to indicate whether a myocardial infarction had occurred recently (that is, within 1 year prior to the time of the follow up interview) (current MI) and a covariate indicating whether a myocardial infarction had occurred at all prior to the time of the follow-up interview, either before or during the trial (Previous MI). The number of patients with EQ-5D data in the follow up period was 1734 and the number of observations was 6203 indicating that each patient on average had their HRQoL measured 3.5 times.

In both treatment strategies HRQoL was improved at 4 months, although an incremental gain of the early interventional strategy compared with the conservative strategy was seen (mean 0.0384, 95 percent confidence interval 0.005 – 0.071) (Table A24). Between 4 and 12 months, HRQoL was improved further in both treatment strategies, although the incremental gain of the early interventional strategy did not reach conventional levels of statistical significance (mean 0.0177, 95 percent confidence interval -0.013 – 0.048). A recent MI was associated with a decrement in HRQoL regardless of treatment allocation (mean -0.0353, 95 percent confidence interval -0.078 – 0.008) and a previous MI prior to study inclusion was associated with a smaller HRQoL decrement (mean -0.0097, 95 percent confidence interval -0.046 – 0.021).

Table A24. Estimated gain in health-related quality of life

Covariate	Coefficient	Standard error	95 % Confidence interval
D4i*	0.0384	0.0168	0.0054 to 0.0714
D12	0.0383	0.0076	0.0234 to 0.0533
D12i*	0.0177	0.0154	-0.0126 to 0.0480
Previous MI	-0.0097	0.0156	-0.0404 to 0.0209
Current MI	-0.0353	0.0220	-0.0784 to 0.0078
Constant	0.0442	0.0126	0.0195 to 0.0689
Between patient standard error (σ_u)		0.295	
Within patient standard error (σ_e)		0.183	
Fraction of variance due to u_i (ϱ)		0.722	

*Note that coefficients represent the gain in utility in the early interventional strategy over and above that of the conservative strategy.

In a similar manner to the cost analysis, a number of assumptions were necessary in order to transfer the HRQoL estimates to quality-adjustment weights for different states in the Markov structure. Employing the baseline utility estimates and changes at 4 and 12 months for the conservative and interventional strategies, respectively, a mean utility at 4 and 12 months could be determined for each strategy. In the No event state in the Markov structure we used the mean of these two values for the first year and the absolute value at 12 months for the second and subsequent years. If no myocardial infarction occurred, a conservative assumption of no difference in HRQoL between the two strategies after 12 months was employed. Applying the coefficient for the current MI covariate to the baseline utilities provided an estimate of the utility to be attached to the first year in the Post MI state. The previous MI covariate was applied to the baseline utility to provide a utility for the second and subsequent years in the Post MI state.

Details of the probabilistic analysis

The model was evaluated for 60 Markov cycles (years) implying that all hypothetical individuals would, in effect, be in the Dead state at the termination of the analysis regardless of the chosen starting age of the cohort. In each simulation in the probabilistic analysis [8], parameter values were drawn randomly from the defined probability distributions and the cohort of hypothetical individuals was run through the model and mean costs and

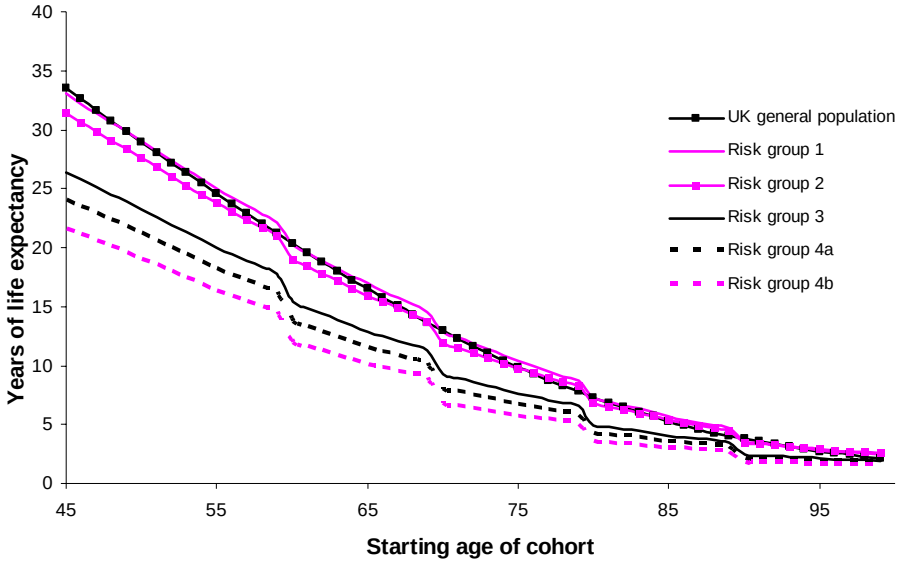
health outcomes calculated for both strategies. This procedure was repeated 5000 times generating 5000 estimates of mean costs and mean effects for both strategies. The expected costs and effects for each treatment strategy are the mean of these 5000 simulations [140]. The expected costs and effects are then combined to an incremental cost-effectiveness ratio.

As the statistical models were based on individual-patient data it was possible to estimate correlations between parameters as well as means and standard errors to be employed in the probabilistic analysis. The Cholesky decomposition matrix, **T**, is derived from the variance- covariance matrix, **V**, such that **TT′=V**. A vector of correlated parameters, **x**, with variance and covariance corresponding to the variance-covariance matrix, can be estimated from the following equation **x=y+Tz**, where **y** is the vector of parameter means and **z** is a vector of independent random draws from the standard normal distribution [28,138]. The distributional assumptions employed in the analysis were multivariate normality of the log-odds scale for the logistic models, multivariate normality of the log hazard scale for the survival-analysis model, and multivariate normality on the raw cost and HRQOL scales for costs and QALYs, respectively.

Model validation

Several analyses were performed to assess the validity of the model. A good indicator of overall validity is to investigate the predicted undiscounted life expectancy from the model. The results of this analysis are shown in Figure A12. Predicted life expectancy for the illustrative patient characteristics with different starting ages of the cohort is shown in the figure together with the life expectancy of the general population in the UK. As expected, predicted life expectancy decreases when the analysed risk groups have a higher risk at baseline. It can be seen in the figure that the estimated life expectancy of patients at low risk (first quartile) is similar to the general population which was also expected.

Figure A12. Predicted life expectancy for different risk profiles and the general UK population



Illustrative patients based on predicted risk of death or MI as defined in RITA 3 represent each risk group [62].

In another check of model validation, the predicted number of events in the model after 5 years was compared with the number of events reported in RITA 3 (where results from 5 years follow-up were reported). In this analysis, the treatment effect observed in RITA 3 was employed and the covariates included in the risk equations were set at their mean value in the trial. Under these circumstances, the predicted number of events and odds ratios from the model is expected to be relatively close to those reported in RITA 3. The results are shown in Table A25. The model slightly underestimates the number of cardiovascular deaths but appear to predict the events in the RITA trial with reasonable precision. The odds ratios from the model are very similar to those observed in RITA 3. The marginally higher odds ratios observed in the model for some outcomes indicate that the results of the model do not appear to bias the results in favour of the early interventional strategy.

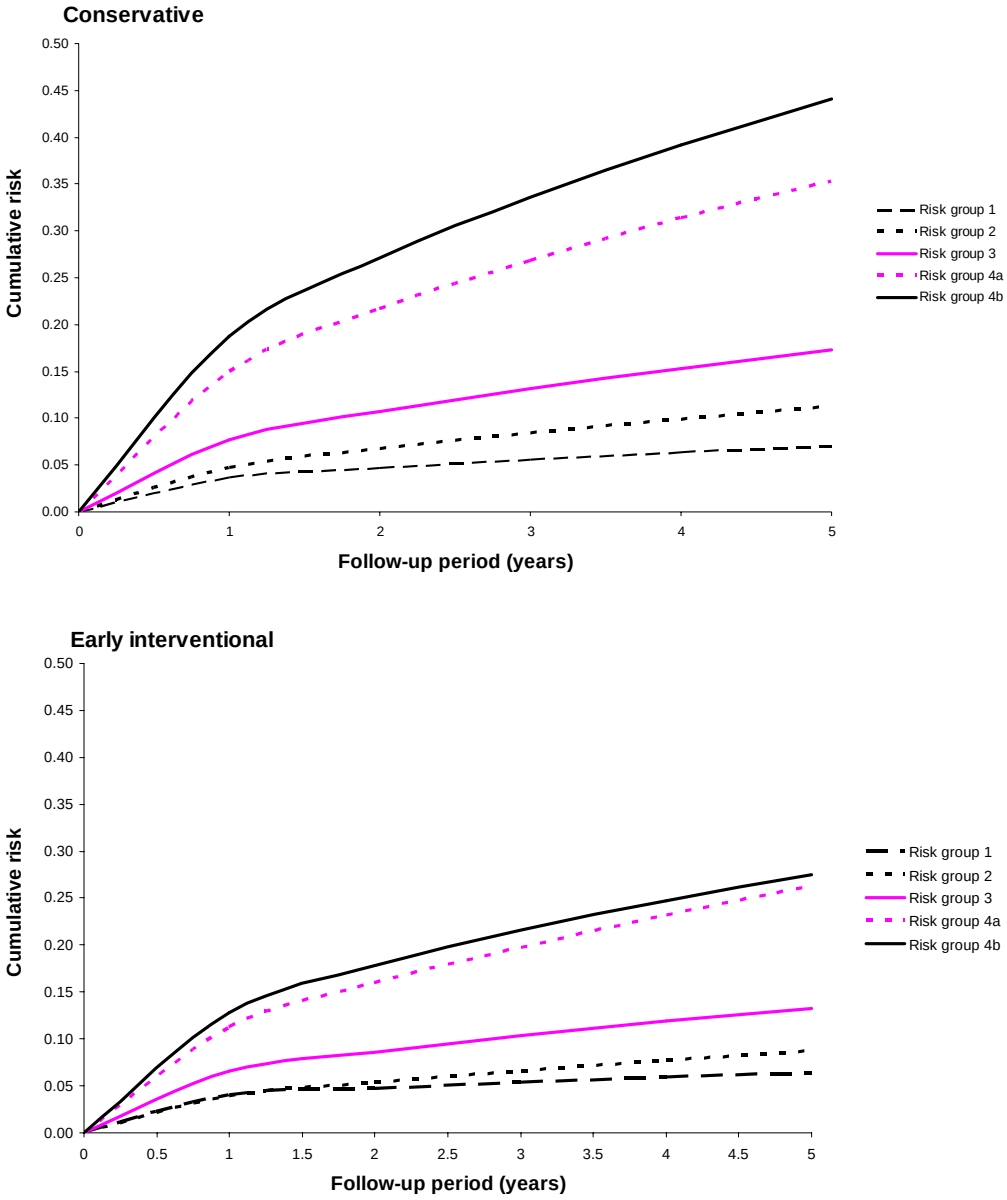
Table A25. Predicted number of events and odds ratios from the model compared with the results reported in RITA 3

	Interventional	Conservative	Odds ratio
Death/MI			
RITA 3 trial	142	178	0.78
Model	137	171	0.79
CVD/MI			
RITA 3 trial	105	139	0.74
Model	99	133	0.74
Death			
RITA 3 trial	102	132	0.76
Model	91	114	0.79
CVD			
RITA 3 trial	62	90	0.68
Model	53	76	0.70

CVD: cardiovascular death. MI: myocardial infarction.

The estimated cumulative risk of a composite endpoint of death or MI in different risk groups is shown in Figure A13. Again, the illustrative patients in each quartile of risk defined in RITA 3 are used in the analysis. The model appears to predict this outcome with reasonable precision in the different risk groups as the cumulative risk curves correspond well with those reported in RITA 3 (figure 5 in the clinical report [62]).

Figure A13. Cumulative risk of the composite endpoint of death or myocardial infarction in different risk groups



Illustrative patients based on predicted risk of death or MI as defined in RITA 3 represent each risk group [62].

Several tests were also performed to check for errors in programming and incorporation of data into the model. In the simplest of these tests no treatment effect was included in the model, i.e. the odds and hazard ratios were set to 1. This yielded the expected results of no difference in life-expectancy between the treatment strategies. Further excluding any differences in costs and health-related quality of life yielded the expected results of no difference at all in costs and health outcome in a lifetime perspective between the two treatment strategies.

Endarterectomy in patients with asymptomatic carotid artery stenosis

The model structure is well described in Paper IV. This section provides a description of the data sources and how data was incorporated in the model. Furthermore, detailed results of the value-of-information analysis are provided and some results of the analyses performed to validate the model.

Data

Outcome of carotid endarterectomy

The outcome of endarterectomy was estimated using data from a population-based registry in Sweden [141]. Applying this non-trial evidence for this parameter was considered to provide a representative estimate of the outcome of carotid endarterectomy in routine clinical practice Sweden. This approach was facilitated as the clinical report from the ACST trial reported rates of non-perioperative strokes [70], thus making it possible to combine data of perioperative outcomes from other sources with trial data. In the Swedish registry, the outcome of 671 endarterectomies performed in patients with an asymptomatic lesion between 1994 and 2003 was available. Strokes classified as transient or permanent in the registry were assumed to correspond to the definitions of non-disabling and disabling strokes, respectively. The results are shown by gender in Table A26. It should be noted that the results by gender was provided by doctor Kragsterman through personal communication as the original source reported combined results for men and women [141].

Table A26. Outcome of endarterectomy in patients with asymptomatic carotid artery stenosis in Sweden between 1994 and 2003

	Men	Women
Total number of endarterectomies	429	242
Number (%) of patients with no event	422 (98.3)	233 (96.2)
Number (%) of non-disabling strokes	3 (0.7)	4 (1.7)
Number (%) of disabling strokes	2 (0.5)	4 (1.7)
Number (%) of deaths	2 (0.5)	1 (0.4)

For the probabilistic analysis, Dirichlet distributions were defined for this parameter using the data reported in Table A26 [142]. Dirichlet(422,3,2,2) was defined for men, yielding point estimates of 0.983, 0.007, 0.005 and 0.005 for the probability of no event, non-disabling stroke, disabling stroke and death, respectively. Corresponding distribution for women was a Dirichlet(233,4,4,1) with point estimates of 0.962, 0.017, 0.017 and 0.004 for the probability of no event, non-disabling stroke, disabling stroke and death, respectively.

Risk of non-perioperative stroke in the BMT strategy

The baseline risk, i.e., the risk of a non-perioperative stroke in the No event state for patients in the BMT strategy, was estimated from the Swedish patients randomised to BMT in the ACST trial. These patients were assumed to best reflect the baseline risk of patients in Sweden. The number of non-perioperative strokes in the BMT arm and time at risk are shown in Table A27.

Table A27. Rates of non-perioperative stroke in the Swedish patients randomised to best medical treatment in the ACST trial

	Men	Women
Number of strokes	18	7
Time at risk	640	416
Yearly rate	0.0281	0.0168

Parametric survival analyses were performed in order to investigate if the risk of stroke increased or decreased with respect to time elapsing from randomisation [127], but no evidence was found of a changing hazard during the five years of trial follow-up. Therefore, a constant hazard was used in the

model. The survival analysis also indicated that age had virtually no effect on the estimated hazards, whereas baseline risk differed between men and women. For the probabilistic analysis, Gamma distributions were defined for the rates of a non-perioperative stroke with the BMT strategy. Gamma(18,640) and Gamma(7,416) were defined for men and women, respectively, yielding a yearly probability of non-perioperative stroke in the No event state of 0.029 for men and 0.019 for women.

Relative risk of non-perioperative stroke with CEA compared with BMT

Once controlling for baseline risk it was considered appropriate to employ data from all patients randomised in the ACST trial to estimate the relative risk of a non-perioperative stroke with CEA compared with BMT. The reported relative risk of non-perioperative stroke was 0.345 [70]. For the probabilistic analysis, normality was assumed on the log scale employing a standard error for the log relative risk of 0.175 [70]. Although there was some indication of a slightly lower (more favourable) relative risk for men compared with women, and similarly for younger compared with older patients, there was little support for these interactions between treatment effect and baseline risk. Hence the often used approach of a common treatment effect, but permitting baseline risk to vary by different risk groups (in this case gender), was employed in this study. In the base-case analysis, a conservative assumption of no treatment effect after the five years of trial follow-up was employed. Different assumptions concerning the duration of the treatment effect after the five years of trial follow-up were investigated in alternative scenarios.

Outcome of non-perioperative strokes

The outcome of a non-perioperative stroke was estimated from the Swedish patients in the ACST trial. Of the 32 non-perioperative strokes observed at 5 years of follow-up 29 were classified; with 7, 8 and 14 being fatal, disabling and non-disabling, respectively. There was little data available to estimate the outcome of non-perioperative stroke in different subgroups for this parameter. A Dirichlet distribution, Dirichlet(7,8,14), was defined for this parameter yielding point estimates of 0.241, 0.276 and 0.483 of a non-perioperative stroke being fatal, disabling and non-disabling, respectively.

Mortality not related to stroke

Data from the Swedish Vascular Registry (SWEDVASC) [91] was used to estimate mortality from other causes than stroke in patients with an asymptomatic carotid artery stenosis. Rather than employing standard

mortality rates from national lifetables, this approach was used in order to account for the potentially higher mortality risk in patients with an asymptomatic lesion due to the presence of cardiovascular disease. A total of 859 patients that had not died within 30 days of carotid endarterectomy for an asymptomatic lesion were included in this analysis. It was assumed that mortality in patients surviving more than 30 days post surgery would be representative of mortality in this population. A Weibull time-to-event proportional hazards model was estimated [127]. The results of the Weibull model are shown in Table A28. As expected, the ancillary (Gamma) parameter was above 1 indicating an increasing hazard over time. Also note that the gender variable was far from significant (hazard ratio = 0.968, 95 percent confidence interval 0.726 - 1.292) and was thus dropped from the final Weibull model.

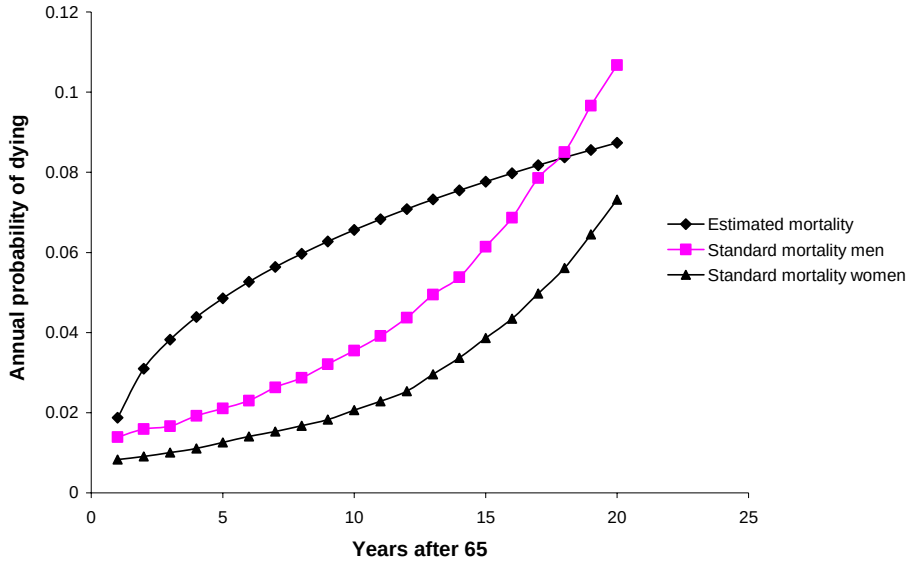
Table A28. Weibull model for 30-day survivors of carotid endarterectomy for an asymptomatic lesion

Variable	Coefficient	95 % Confidence interval
Age	1.069	1.047 – 1.090
Constant*	0.0003	0.0001 – 0.001
Gamma**	1.414	1.270 – 1.573

*Constant is the hazard at time zero.
**Shape parameter in the Weibull model where a coefficient below (above) 1 indicates a decreasing (increasing) hazard over time.

The mortality rates predicted from the Weibull model were converted to annual probabilities of death from other causes than stroke [28]. The correlation between coefficients in the regression model was maintained in the probabilistic assessment employing Cholesky decomposition assuming multivariate normality on the log scale [28]. The estimated probabilities for 65-year-old men and women are shown in Figure A14. It is shown in the figure that the difference between the estimated mortality for patients with an asymptomatic carotid artery stenosis and standard mortality is decreasing as patients get older and are at increased risk of dying from other causes. In the decision-analytic model we used the estimated risk of death as long as it was above standard mortality and then switched to standard mortality. An alternative scenario employed standard mortality from national lifetables rather than the estimated mortality.

Figure A14. Probabilities of non-stroke death in the population with carotid artery stenosis (65-year-olds)



Life-expectancy post stroke

Other sources [143] have shown a relatively high risk of death the first year after a stroke. This risk appears to decline in subsequent years after the stroke. Data from SWEDVASC [91] on stroke survivors was used to estimate the survival prognosis of these patients. The estimated prognosis of stroke survivors was then compared with the estimated mortality in the population with asymptomatic carotid artery stenosis in order to determine the excess mortality risk associated with having experienced a stroke. The first year after a disabling stroke, the excess risk was about 3 for men and 1.5 for women. The second and subsequent years after a disabling stroke, no excess risk was seen for women, whereas the excess risk was halved compared with the first year after the stroke for men. A hazard ratio of 3 for men and 1.5 for women was thus applied to the estimated Weibull model in Table A28 to determine the probability of death first year after stroke. For the probabilistic analysis normal distributions were defined for the log hazard ratio: Normal(1.10, 0.146) for men and Normal(0.41,0.146) for women. For patients suffering a non-disabling stroke no adjustment of the estimated mortality was made.

Costs

The estimated cost of carotid endarterectomy was 63 400 SEK. This estimate was based on performance-based costing reflecting actual resource use for carotid endarterectomy in the county of Östergötland Sweden (http://www.lio.se/upload/16047/Prislista%202006.pdf [accessed February 22 2007]). For the probabilistic analysis a Gamma distribution, Gamma(161,394), was defined based on a standard error of 5 000 SEK. The estimated standard error was based on previous estimates of comprehensive modelling of costs of surgical procedures [144].

The annual cost of best medical treatment was estimated at 2 620 SEK. This cost included a doctor's visit and costs of pharmaceutical treatment. This cost was not varied in the probabilistic analysis.

A literature review was undertaken to obtain estimates of costs associated with the post-stroke states in the model. We searched PubMed using a free-text search of 'costs AND stroke AND Sweden'. Most recent search was performed in February 2007. This search yielded 45 references of which 8 articles were scrutinised in more detail. One study provided comprehensive information on costs post stroke in Sweden based on recent data sources [143]. In this study the average total cost the first year after a stroke was 155 000 SEK, including hospitalisations, drugs, outpatient visits, rehabilitation, nursing home and domestic aid [143]. The second and subsequent years after a stroke, the estimated annual cost was 60 000 SEK. It should be noted that these estimates are averages over patients suffering disabling and non-disabling stroke and the costs are expected to be substantially higher in the patients suffering a disabling stroke. In the study by Ghatnekar and colleagues [143], 60 percent of the strokes were non-disabling and 40 percent were disabling (personal communication, Terent). Based on this information, costs of 240 000 SEK and 100 000 SEK was assigned for the first year after a disabling and non-disabling stroke, respectively. The study by Ghatnekar et al reported large standard deviations for the individual cost components in their calculations of total costs. However, standard errors of the total costs were not reported. For the present analysis we assumed large standard errors to reflect the substantial uncertainty associated with these estimates. Gamma distributions, Gamma(23,10417) and Gamma(25,4000) were defined for the costs the first year after a disabling and non-disabling stroke, respectively. For the second and subsequent years after a stroke an annual cost of 110 000 SEK and 20 000 SEK was estimated for disabling and non-disabling stroke, respectively

employing Gamma(19,5682) and Gamma(16,1250) distributions for the probabilistic analysis.

QALYs

Age-adjusted quality-adjustment weights, or utilities, from a normal population in Sweden were used for patients in the No event state and are shown in Table A29 together with the distributions employed in the probabilistic analysis [115]. The Beta distributions were fitted using methods-of-moment techniques employing the reported means and standard errors [32].

Table A29. Utilities for patients in the No event state

	Men			Women		
Age	**Mean**	**SE**	**Distribution**	**Mean**	**SE**	**Distribution**
69 or younger	0.83	0.012	Beta(812,166)	0.78	0.015	Beta(594,168)
70 – 79	0.81	0.018	Beta(384,90)	0.78	0.017	Beta(462,130)
80 or older	0.74	0.037	Beta(103,36)	0.74	0.026	Beta(210,74)

SE: standard error.

A literature review was undertaken to obtain estimates of health-related quality of life associated with the post-stroke states in the model. We searched PubMed using free-text search of 'stroke AND QALY' and 'post-stroke AND health-related quality of life'. Most recent search was performed in February 2007. This search yielded 169 references of which 9 articles were scrutinised in detail. Two papers reported health-related quality of life, or utilities, for health states defined according to the health states in the present model [145,146]. One study employed a direct time-trade off technique [145] and one used the EQ-5D instrument [146] to establish utilities for disabling (modified Rankin score 3, 4 or 5) and non-disabling (modified Rankin score 0, 1 or 2) stroke. Both studies showed that the average utility with a post non-disabling stroke was not lower than the utilities of individuals in the normal population. Hence, no decrement in utility was assumed for patients in the post-disabling stroke state. For patients with a disabling stroke, a substantial loss of utility was seen in both studies. Haake and colleagues [146] reported a mean utility of 0.44 and Duncan and colleagues reported [145] a mean utility of 0.54 for patients with a disabling stroke, indicating a decrement in quality of life of about 0.35 from the utility of the normal population. The uncertainty around these estimates was not clearly reported in the studies but the standard error

of the decrement appeared to be about 0.1. Based on this information a Gamma distribution, Gamma(12.25,0.03), was employed for the probabilistic analysis.

Detailed results of the value-of-information analysis

Value of information for the decision

Detailed results of the value of information for the decision to adopt the CEA strategy are shown in Tables A30 and A31 for men and women, respectively. The second column of the tables shows the ICERs. Column 3 shows the optimal treatment decision based on current information, where the CEA strategy should be adopted if the ICER is below the willingness to pay for a QALY and the BMT strategy should be adopted if the ICER is above the willingness to pay for a QALY. This strategy is referred to as the a priori strategy in the tables. The fourth column shows the error probability, or the proportion of iterations in the probabilistic assessment that the a priori strategy is not cost-effective. When CEA is the a priori strategy, this is one minus the probability of CEA being cost-effective and when CEA is not the a priori strategy this is the probability of CEA being cost-effective at a willingness to pay for a QALY of 500 000 SEK. Note that for men (Table A30) the error probability is highest for 73-year-old patients as the ICER is close to the willingness to pay for a QALY, indicating that the adoption decision is associated with large uncertainty. The fifth column shows the estimated EVPI per patient. This estimate is a function of the error probability and the consequence of an error. The consequence of an error is the net benefit forgone when the a priori decision turned out to be wrong. The sixth column in Tables A30 and A31 shows the estimated number of patients in each subgroup facing this decision problem during a year. A time horizon of 10 years was assumed and a discount rate of 3 percent was used when estimating the number of patients diagnosed with an asymptomatic lesion over the next ten years (shown in column 7). The last column shows the total EVPI for the decision for each subgroup, which is the EVPI per patient multiplied by the effective population.

Table A30. Expected value of perfect information for the decision (men)

Age	ICER	A priori strategy	Error probability	EVPI patient	Yearly population	Effective population	EVPI population
55	215 894	CEA	0.138	2 985	6	53	157 378
56	224 181	CEA	0.146	3 145	6	53	165 813
57	232 984	CEA	0.155	3 321	6	53	175 072
58	242 346	CEA	0.164	3 517	6	53	185 404
59	252 311	CEA	0.175	3 734	6	53	196 853
60	262 934	CEA	0.184	3 973	10	88	349 038
61	274 272	CEA	0.198	4 235	10	88	372 115
62	286 392	CEA	0.216	4 533	10	88	398 238
63	299 376	CEA	0.236	4 872	10	88	428 053
64	313 309	CEA	0.253	5 257	10	88	461 902
65	328 292	CEA	0.273	5 684	12	105	599 335
66	344 283	CEA	0.292	6 154	12	105	648 819
67	361 301	CEA	0.318	6 670	12	105	703 204
68	379 511	CEA	0.343	7 244	12	105	763 725
69	398 898	CEA	0.372	7 875	12	105	830 311
70	419 595	CEA	0.396	8 558	16	141	1 203 036
71	442 574	CEA	0.431	9 345	16	141	1 313 686
72	467 583	CEA	0.468	10 237	16	141	1 439 092
73	495 246	CEA	0.512	11 247	16	141	1 581 143
74	525 850	BMT	0.448	9 901	16	141	1 391 826
75	559 836	BMT	0.400	8 199	8	70	576 315
76	596 642	BMT	0.355	6 693	8	70	470 427
77	636 419	BMT	0.309	5 361	8	70	376 789
78	677 782	BMT	0.270	4 244	8	70	298 337
79	722 817	BMT	0.225	3 271	8	70	229 883
80	770 344	BMT	0.181	2 476	2	18	43 507
81	829 091	BMT	0.137	1 783	2	18	31 334
82	896 288	BMT	0.106	1 239	2	18	21 775
83	977 646	BMT	0.074	794	2	18	13 946
84	1 072 334	BMT	0.048	476	2	18	8 366

Note: Error probability and EVPI are evaluated at a willingness to pay for a QALY of 500 000 SEK. Precise figures are reported in the last column. Due to rounding errors the results in this column may not be identical to multiplying the reported values in columns 5 by those in column 7.

Table A31. Expected value of perfect information for the decision (women)

Age	ICER	A priori strategy	Error probability	EVPI patient	Yearly population	Effective population	EVPI population
55	1 822 039	BMT	0.173	5 719	2	18	100 490
56	1 893 631	BMT	0.164	5 264	2	18	92 505
57	1 971 631	BMT	0.156	4 825	2	18	84 783
58	2 056 824	BMT	0.145	4 404	2	18	77 387
59	2 150 106	BMT	0.136	4 002	2	18	70 318
60	2 252 539	BMT	0.126	3 619	4	35	127 183
61	2 365 385	BMT	0.116	3 258	4	35	114 507
62	2 490 122	BMT	0.110	2 916	4	35	102 497
63	2 628 567	BMT	0.101	2 593	4	35	91 146
64	2 782 887	BMT	0.095	2 286	4	35	80 348
65	2 955 765	BMT	0.086	1 999	6	53	105 372
66	3 150 520	BMT	0.078	1 736	6	53	91 515
67	3 371 379	BMT	0.070	1 495	6	53	78 820
68	3 623 759	BMT	0.062	1 278	6	53	67 352
69	3 914 768	BMT	0.055	1 083	6	53	57 098
70	4 253 950	BMT	0.047	912	6	53	48 071
71	4 654 399	BMT	0.041	762	6	53	40 194
72	5 134 696	BMT	0.035	629	6	53	33 145
73	5 722 098	BMT	0.031	510	6	53	26 906
74	6 458 387	BMT	0.027	407	6	53	21 476
75	7 407 869	BMT	0.022	318	4	35	11 171
76	8 602 208	BMT	0.017	245	4	35	8 619
77	10 115 491	BMT	0.013	189	4	35	6 632
78	12 031 408	BMT	0.011	144	4	35	5 078
79	14 410 206	BMT	0.008	112	4	35	3 949
80	17 349 482	BMT	0.006	89	2	18	1569
81	22 607 946	BMT	0.005	69	2	18	1204
82	31 845 002	BMT	0.004	51	2	18	893
83	50 998 665	BMT	0.003	36	2	18	637
84	120 706 356	BMT	0.002	24	2	18	430

Note: Error probability and EVPI evaluated at a willingness to pay for a QALY of 500 000 SEK. Precise figures are reported in the last column. Due to rounding errors the results in this column may not be identical to multiplying the reported values in columns 5 by those in column 7.

Value of information for parameters

The value of information for model parameters is shown in Tables A32 and A33 for men and women, respectively.

Table A32. Expected value of perfect information for parameters (men)

Age	Relative Risk	Baseline Risk	Baseline Risk+5	Outcome CEA	Outcome Stroke	Mort. asympt.	Mort. stroke	Cost CEA	Cost stroke	Utilities
55	867	28 706	0	31 704	13 797	0	0	0	0	0
56	1 102	32 057	0	33 231	15 881	0	0	0	0	0
57	1 332	36 206	0	35 101	18 274	0	0	0	0	0
58	1 565	40 949	0	37 438	20 988	0	0	0	0	0
59	2 227	46 713	0	40 190	21 805	0	0	0	0	0
60	4 245	88 718	0	72 507	46 755	0	0	0	0	0
61	5 168	101 316	0	78 849	53 828	0	0	0	0	0
62	5 287	115 787	0	86 600	62 555	0	0	0	0	0
63	6 518	133 648	0	96 056	74 068	0	0	0	0	0
64	10 700	185 697	0	129 488	107 219	0	0	0	0	0
65	15 692	215 916	0	147 318	129 635	0	0	0	0	0
66	23 521	252 749	0	167 954	157 916	0	0	0	0	0
67	34 751	300 332	0	193 285	191 153	0	0	0	0	0
68	51 586	356 722	0	224 623	231 373	0	0	196	0	0
69	74 723	421 218	0	262 883	279 522	0	0	872	0	0
70	147 691	659 543	0	410 604	338 764	0	0	6 295	0	72
71	216 795	773 952	98	492 161	551 527	993	0	33 509	0	5 189
72	312 303	904 593	2 689	598 695	673 351	15 526	0	101 036	2 393	46 234
73	447 906	1 062 747	50 506	729 888	821 664	110 347	21 143	250 595	77 960	184 775
74	266 552	943 606	3 670	525 343	645 892	14 405	0	127 953	7 235	69 836
75	59 043	364 363	0	161 287	223 443	47	0	19 837	0	7 347
76	19 309	272 930	0	86 558	143 806	0	0	4 142	0	461
77	3 901	148 320	0	37 357	84 535	0	0	513	0	0
78	397	139 616	0	10 348	45 721	0	0	0	0	0
79	0	94 435	0	1 055	21 357	0	0	0	0	0
80	0	15 448	0	0	2 104	0	0	0	0	0
81	0	9 205	0	0	312	0	0	0	0	0
82	0	4 653	0	0	0	0	0	0	0	0
83	0	1 940	0	0	0	0	0	0	0	0
84	0	732	0	0	0	0	0	0	0	0
55-84	1 713 181	7 752 817	56 963	4 690 523	4 977 245	141 318	21 143	544 948	87 588	313 914

Relative risk: relative risk of non-perioperative stroke with the CEA strategy compared with BMT. **Baseline risk**: risk of non-perioperative stroke with the BMT strategy. **Baseline risk +5**: risk of non-perioperative stroke with BMT after year 5. **Outcome of CEA**: perioperative death or stroke (disabling or non disabling**).** **Outcome stroke**: proportion of strokes being fatal, non disabling and disabling**.** **Mort. asympt**: estimated mortality in the population with asymptomatic stenosis. **Mort. stroke**: mortality post stroke**.** **Cost CEA**: cost of endarterectomy. **Cost stroke**: costs in the post-stroke states. **Utilities**: utilities associated with health states in the model.
EVPPI is estimated at a willingness to pay for a QALY of 500 000 SEK.

Table A33. Expected value of perfect information for parameters (women)

Age	Relative Risk	Baseline risk	Baseline Risk+5	Outcome CEA	Outcome Stroke	Mort. asympt.	Mort. stroke	Cost CEA	Cost stroke	Utilities
55	0	48 473	0	7 590	373	0	0	0	0	0
56	0	44 113	0	5 854	172	0	0	0	0	0
57	0	39 940	0	4 342	36	0	0	0	0	0
58	0	35 912	0	3 049	48	0	0	0	0	0
59	0	32 088	0	2 053	0	0	0	0	0	0
60	0	57 071	0	2 705	0	0	0	0	0	0
61	0	50 373	0	1 717	0	0	0	0	0	0
62	0	44 287	0	1 024	0	0	0	0	0	0
63	0	38 591	0	473	0	0	0	0	0	0
64	0	33 288	0	201	0	0	0	0	0	0
65	0	43 011	0	83	0	0	0	0	0	0
66	0	36 984	0	0	0	0	0	0	0	0
67	0	31 323	0	0	0	0	0	0	0	0
68	0	26 276	0	0	0	0	0	0	0	0
69	0	21 790	0	0	0	0	0	0	0	0
70	0	17 719	0	0	0	0	0	0	0	0
71	0	13 891	0	0	0	0	0	0	0	0
72	0	10 501	0	0	0	0	0	0	0	0
73	0	7 607	0	0	0	0	0	0	0	0
74	0	5 214	0	0	0	0	0	0	0	0
75	0	2 166	0	0	0	0	0	0	0	0
76	0	1 265	0	0	0	0	0	0	0	0
77	0	788	0	0	0	0	0	0	0	0
78	0	593	0	0	0	0	0	0	0	0
79	0	450	0	0	0	0	0	0	0	0
80	0	158	0	0	0	0	0	0	0	0
81	0	90	0	0	0	0	0	0	0	0
82	0	24	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0
55-84	0	643 986	0	29 091	629	0	0	0	0	0

Relative risk: relative risk of non-perioperative stroke with the CEA strategy compared with BMT. **Baseline risk**: risk of non-perioperative stroke with the BMT strategy. **Baseline risk +5**: risk of non-perioperative stroke with BMT after year 5. **Outcome of CEA**: perioperative death or stroke (disabling or non disabling). **Outcome stroke**: proportion of strokes being fatal, non disabling and disabling**.** **Mort. asympt**: estimated mortality in the population with asymptomatic stenosis. **Mort. stroke**: mortality post stroke. **Cost CEA**: cost of endarterectomy. **Cost stroke**: costs in the post-stroke states. **Utilities**: utilities associated with health states in the model.
EVPPI is estimated at a willingness to pay for a QALY of 500 000 SEK.

The value of sample information

In this simple example of expected value of sample information (EVSI), the focus is on 74-year-old men and the baseline risk of non-perioperative stroke. The expected value of perfect partial information (EVPPI) for this parameter was approximately 1 000 000 SEK for 74-year-old men. The prior distribution for the baseline risk was a Gamma distribution, Gamma(18,640). Following the methods outlined by Ades et al. [45], a value from this distribution is sampled, which we denote θ_I^i. Given this value, the outcome of the proposed study is simulated. Assuming *n* patients with a diagnosis of asymptomatic carotid artery stenosis are to be followed up for *k* years, the simulated study outcome follows a Poisson distribution. The Poisson event counts, which we denote *e*, can be drawn from Poisson(θ_I^i,*nk*), where θ_I^i is the prior event rate and *nk* is the total number of patient years of follow-up in the new study. The prior distribution for the baseline risk is then updated with the simulated event count and the total number of patient years of follow-up yielding a Gamma(18+*e*,640+*nk*) distribution. This updated Gamma distribution is then applied in the decision-analytic model where net benefit of both treatment strategies is established. This procedure is then repeated for a large number of simulations in order to determine the EVSI for this particular trial design, i.e., this particular *nk*. In this simplified calculation we assumed that it would be relatively easy to set up a registry study following patients with a diagnosis of asymptomatic carotid artery stenosis at a fixed cost of 100 000 SEK, with an additional marginal cost of 1 000 SEK for each patient year of follow-up. The EVSI, total costs of sampling and expected net benefit of sampling (ENBS) are shown in Figure A15 for different study designs (i.e., different *nk*).

Figure A15. EVSI, ENBS and total costs of sampling for baseline risk of non-perioperative stroke (74-year-old men)

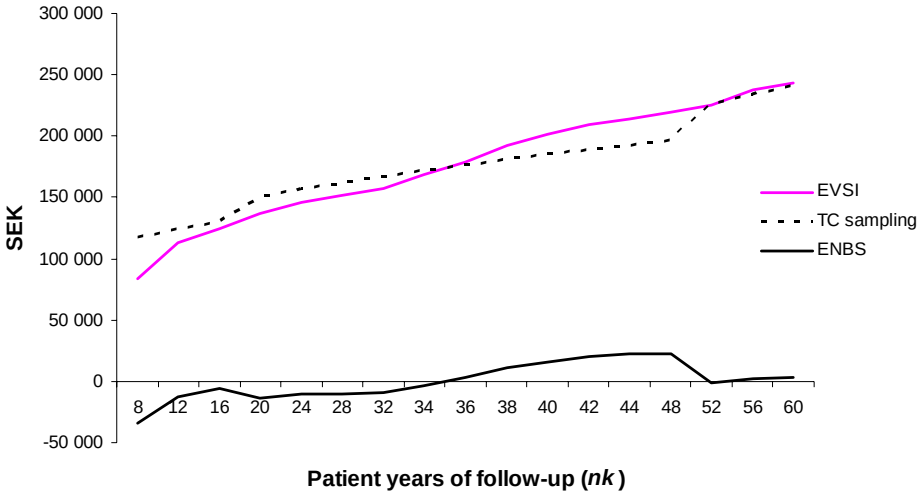
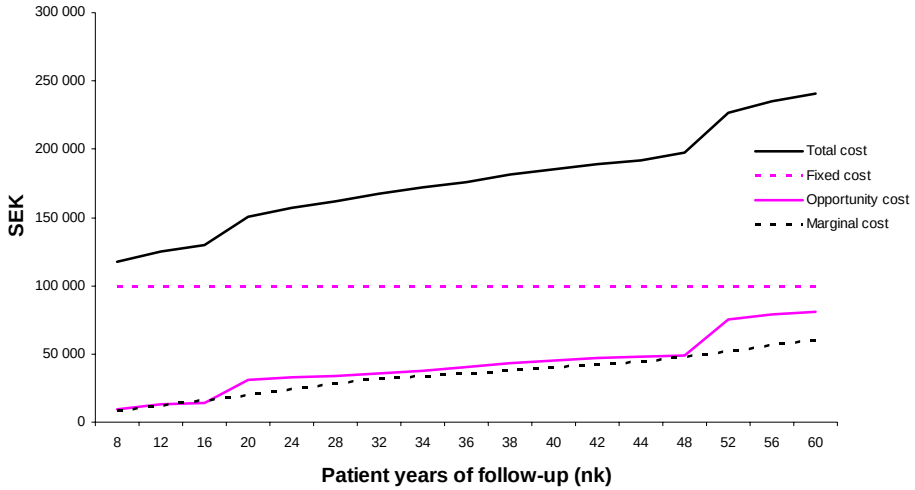


Figure A15 reveals that the EVSI increases with a larger sample (more patient years of follow-up), reflecting the fact that more sample information lead to a more informed adoption decision, ultimately leading to improved expected net benefit. In fact, as the sample size increases, the EVSI will tend towards the EVPPI for the parameter. This is intuitive as the EVPPI for the parameters implies an infinite sample. It is also clear from Figure A15 that ENBS is highest at about 44 patient years of follow-up, i.e., this is the maximum of EVSI minus the total cost of sampling. Finally, a few notes regarding the cost function. Details of the cost components are shown in Figure A16.

Figure A16. Expected costs of sampling



The fixed and marginal costs of carrying out the follow-up study are conceptually unproblematic, although their estimation can most likely be improved in a real application. It is important to take the opportunity cost of sampling into account as well. Here, this is the EVSI forgone as the patients enrolled in the study will not be able to benefit from the information generated by the new sample. The estimated number of 74-year-old men diagnosed with asymptomatic carotid artery stenosis was 16 per year. Hence, for any follow-up study requiring less than 16 patient years of follow-up, the estimated 16 patients diagnosed the first year cannot benefit from this information. If more than 16 patient years are required, the next cohort of 74-year-old men cannot benefit from the information as it will not be available when their treatment decision have to be made. This explains the increased opportunity cost after 16 patient years of follow-up. Another increase in this cost is seen at 48 patient years of follow-up as a third cohort of 74-year-old men cannot benefit from this information (first 16 patients followed for 2 years and second cohort of 16 patients for 1 year).

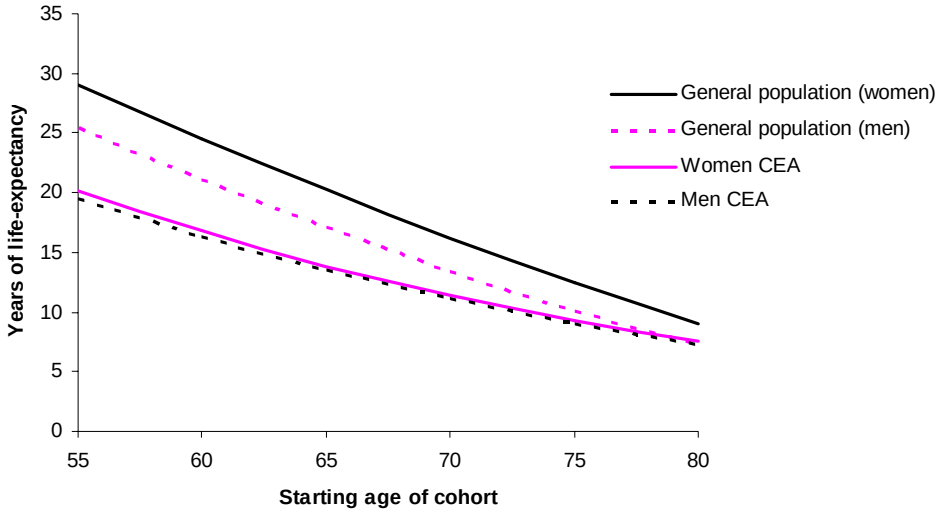
The decision problem in this application further complicates the issues of efficient research design. For example, the information acquired for 74-year-old men will benefit other cohorts as well. Hence, the EVSI shown in Figure A15 is much larger as most cohorts of men will benefit from this information. In order to solve the optimisation problem in this case, we would need to

estimate the EVSI over all cohorts. This means that different types of study set ups are possible. If a constant hazard of non-perioperative stroke over time and across different ages is assumed, as it is in the present model, different types of designs must be considered, taking into account how many patients at certain ages should be enrolled each year and how long they should be followed up. This in turn will have an impact on the opportunity cost of sampling, where the opportunity cost of holding back the a priori strategy for some patients must be incorporated. Note, that for 74-year-old men the a priori strategy is BMT whereas for all men younger than 74, CEA is the a priori strategy. Enrolling these patients into a follow-up study investigating the baseline risk of stroke (in effect the BMT strategy) have further opportunity costs than EVSI forgone, as these patients will not receive the treatment with the highest net benefit during the proposed study.

Model validation

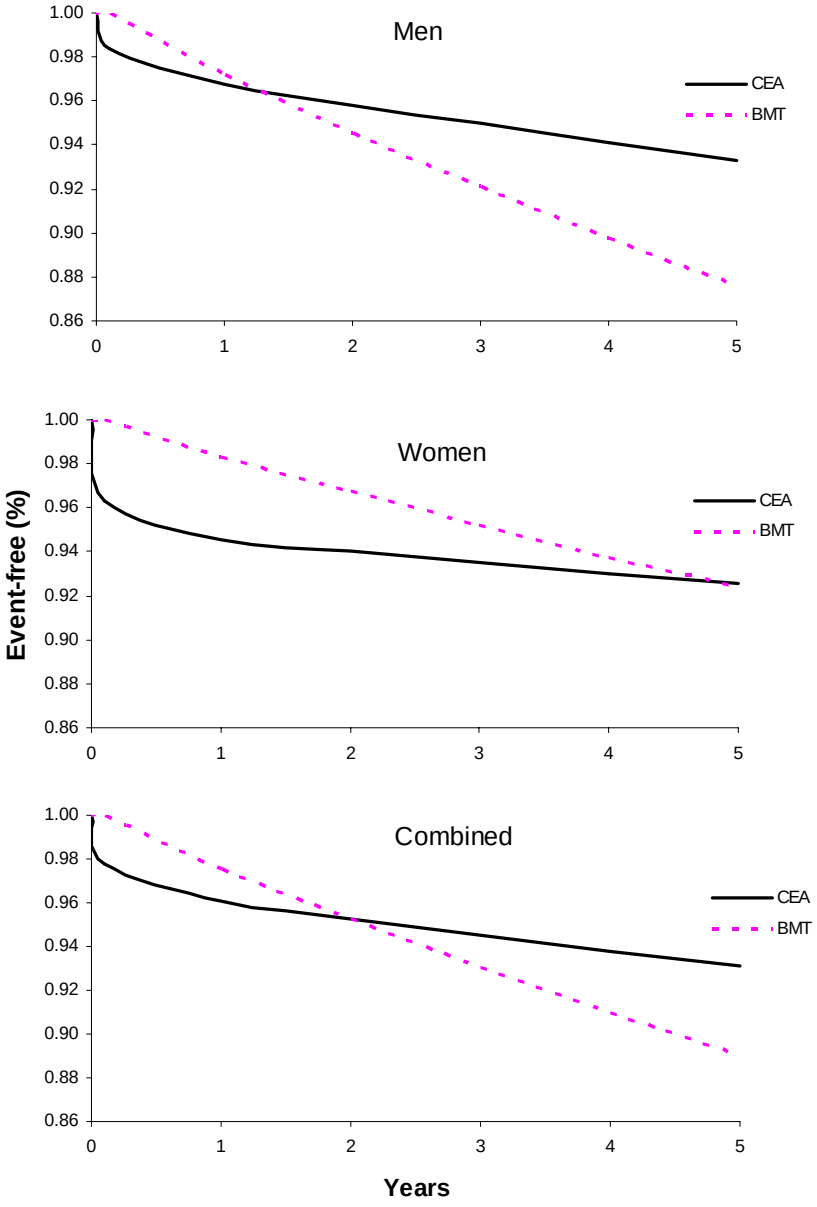
Several analyses were performed to assess the validity of the model. A good indicator of overall validity is to investigate the predicted undiscounted life expectancy from the model. The results of this analysis are shown in Figure A17. Predicted life expectancy for men and women at different ages is shown in the figure together with the life expectancy of the general population in Sweden. As expected, predicted life expectancy is lower than that of the normal population and decreases when the analysed risk groups have a higher starting age.

Figure A17. Predicted life-expectancy for men and women with the CEA strategy and the general Swedish population



The event rates employed in this study are similar to those reported for all patients in the ACST trial [70]. Hence, the predicted number of events after 5 years in the model should be similar to those reported in ACST. The proportion of patients without any major event (stroke or perioperative death) predicted by the model is shown in Figure A18 for 65-year-old men and women, respectively. In the last panel in Figure A18, the results are combined, giving 70 percent weight to men reflecting the proportion of men in the ACST trial. These results correspond well with the results reported in ACST, which is expected if the model is correctly specified and programmed.

Figure A18. Predicted perioperative deaths or any stroke in the model for 65-year-old patients



Several tests were also performed to check for technical flaws such as errors in programming, which is normally referred to as internal validity or consistency [26]. The simplest of these tests include removing the risk of an event during the carotid endarterectomy procedure, leave out the treatment effect on non-perioperative stroke and remove the cost of the endarterectomy. Under these circumstances the two strategies expectedly give exactly the same costs and health outcomes.

ACKNOWLEDGEMENTS

I am grateful to many people who have supported, inspired and encouraged me over the years. I would like to especially acknowledge the following:

Per Carlsson, supervisor, for introducing me to the field of economic evaluation and giving me the opportunity to write this thesis, and for always reminding me of the broader picture when I have been committed to decomposing matrices.

Fredrik Lundgren, co-supervisor, for being a true source of inspiration throughout the work with this thesis, providing invaluable medical expertise, interesting discussions, and many laughs.

Mark Sculpher, co-supervisor, for sharing your vast knowledge and experience in this field and always welcoming me to the Centre for Health Economics in York allowing me to harass your staff.

Karl Claxton, a true inspirer, for enthusiastic and insightful discussions over the years and for providing invaluable advice on many of the issues in this thesis.

Stephen Palmer, for teaching me modelling with great patience, and always helping out with methodological issues and commenting on drafts, including invaluable feedback on earlier drafts of this thesis.

David Epstein, for great collaboration in the work with Paper III and many interesting discussions over the years.

Magnus Janzon, for providing inspiration by just being great, and for always finding a bit of time to teach me cardiology.

Magnus Husberg, for always being helpful and sorting out problems related to computers in general and Excel in particular.

Nathalie Eckard, for providing great support in the writing process, including efforts to teach me English, and if the language in this thesis in any way resembles decent English it is thanks to you.

Thor-Henrik Brodtkorb, Lars Bernfort and Gustav Tinghög, for being great mates, and for providing useful inputs on earlier drafts of the manuscript.

Joakim Ramsberg, for many inspiring discussions over the years, and for providing valuable advice on earlier drafts of the manuscript.

Dorte Gyrd-Hansen and **Anders Wanhainen**, for acting as discussants at a 50 percent seminar and providing many useful inputs.

Lena Hector, for always helping out with all sorts of administrative issues.

Sussanne A Larsson, for sorting out the layout of this book and helping me with the files.

Friends and colleagues at Center for Medical Technology Assessment, Linköping University and Centre for Health Economics, University of York.

The Hammers, for reminding me that a nice pint, football and good mates are important attributes in any utility function. COME ON YOU IRONS!

My Brothers, for being what brothers should be, good old reliable friends.

My Parents, for being true role models giving endless support to your three boys over the years.

Karl and Frans, for being wonderful little kids that make me happy every day.

Elin, for your love, true friendship and 100 percent support, making it possible, and a pleasure, to sort out all everyday challenges together.

Financial support from the Health Council of Östergötland and the National Pharmacy Corporation's fund for research and studies in health economics and social pharmacy is greatly appreciated.

REFERENCES

1. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press; 2005.
2. Gold M, Siegel J, Russell L, Weinstein M. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University press; 1996.
3. Lindley D. *Making Decisions*. 2nd ed. New York: Wiley; 1985.
4. Polsky D, Glick H, Willke R, Schulman K. Confidence intervals for cost-effectiveness ratios: a comparison of four methods. *Health Econ* 1997;6:243-52.
5. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ* 1999;18:341-64.
6. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute For Clinical Excellence (NICE). *Lancet* 2002;360:711-715.
7. National Institute for Clinical Excellence (NICE). *Guide to the Methods of Technology Appraisal*. London: NICE; 2004.
8. Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. *Health Econ* 2005;14:339-47.
9. Griffin S, Claxton K, Hawkins N, Sculpher M. Probabilistic analysis and computationally expensive models: Necessary and required? *Value Health* 2006;9:244-52.
10. Johannesson M, Meltzer D. Some reflections on cost-effectiveness analysis. *Health Econ* 1998;7:1-7.
11. Brouwer W, Koopmanschap M. On the economic foundations of CEA. Ladies and gentlemen, take your positions! *J Health Econ* 2000;19:439-59.
12. Weinstein M, Manning W, Jr. Theoretical issues in cost-effectiveness analysis. *J Health Econ* 1997;16:121-8.
13. Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S. A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme. *Health Technol Assess* 2004;8:1-132.
14. Briggs A. Handling uncertainty in economic evaluation and presenting the results. In: Drummond M, McGuire A, editors. Economic Evaluation in Health Care -Merging Theory with Practice. Oxford New York: Oxford University Press; 2001.

15. Karlsson G, Johannesson M. The Decision Rules of Cost-Effectiveness Analysis. *Pharmacoeconomics* 1996;9:113-120.
16. Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. *Health Econ* 1998;7:723-40.
17. Tambour M, Zethraeus N, Johannesson M. A note on confidence intervals in cost-effectiveness analysis. *Int J Technol Assess Health Care* 1998;14:467-71.
18. Stinnett A, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;18:S68-80.
19. Weinstein M, Toy E, Sandberg E, Neumann P, Evans J, Kuntz K, et al. Modeling for health care and other policy decisions: uses, roles, and validity. *Value Health* 2001;4:348-61.
20. Buxton M, Drummond M, van Hout B, Prince R, Sheldon T. Modelling in Economic Evaluation: an unavoidable fact of life. *Health Econ* 1997;6:217-227.
21. Kassirer J, Angell M. The journal's policy on cost-effectiveness analyses. *N Engl J Med* 1994;331:669-70.
22. Sheldon T. Problem of using modelling in the economic evaluation of health care. *Health Econ* 1996;5:1-11.
23. Weinstein M, Fineberg M. *Clinical Decision Analysis*. Philadelphia: W. B. Saunders Company; 1980.
24. Hjelmgren J, Berggren F, Andersson F. Health Economic Guidelines - Similarities, Differences and Some Implications. *Value Health* 2001;4:225-250.
25. Weinstein M, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value Health* 2003;6:9-17.
26. Sculpher M, Fenwick E, Claxton K. Assessing quality in decision analytic cost-effectiveness models. A suggested framework and example of application. *Pharmacoeconomics* 2000;17:461-77.
27. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Pharmacoeconomics* 2006;24:355-71.
28. Briggs A, Sculpher M, Claxton K. *Decision modelling for health economic evaluation*: Oxford University Press; 2006.
29. Sculpher M, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? *Health Econ* 2006;15:677-87.

30. Ades A, Sculpher M, Sutton A, Abrams K, Cooper N, Welton N, et al. Bayesian methods for evidence synthesis in cost-effectiveness analysis. *Pharmacoeconomics* 2006;24:1-19.
31. Sutton A, Abrams K, Jones D, Sheldon T, Song F. *Methods for Meta-Analysis in Medical Reseach*. Chichester: Wiley; 2000.
32. Briggs A, Goeree R, Blackhouse G, O'Brien B. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Med Decis Making* 2002;22:290-308.
33. Briggs A. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000;17:479-500.
34. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;10:779-87.
35. Fenwick E, O'Brien B, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. *Health Econ* 2004;13:405-15.
36. Severens J, Brunenberg D, Fenwick E, O'Brien B, Joore M. Cost-effectiveness acceptability curves and a reluctance to lose. *Pharmacoeconomics* 2005;23:1207-14.
37. Briggs A, Mihaylova B, Sculpher M, Hall A, Wolstenholme J, Simoons M, et al. The Cost-effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA Study. *Heart* published online 29 Nov 2006;doi10.1136/hrt.2005.086728.
38. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R. Lifetime cost effectiveness of simvastatin in a range of risk groups and age groups derived from a randomised trial of 20,536 people. *Bmj* 2006;333:1145-8.
39. Pratt J, Raiffa H, Schlaifer R. *Introduction to Statistical decision theory*. Cambridge, MA: The MIT press; 1995.
40. Yokota F, Thompson K. Value of information literature analysis: a review of applications in health risk management. *Med Decis Making* 2004;24:287-98.
41. Felli J, Hazen G. Sensitivity analysis and the expected value of perfect information. *Med Decis Making* 1998;18:95-109.
42. Felli J, Hazen G. A Bayesian approach to sensitivity analysis. *Health Econ* 1999;8:263-8.
43. Claxton K. Bayesian approaches to the value of information: implications for the regulation of new pharmaceuticals. *Health Econ* 1999;8:269-74.
44. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. *Health Econ* 1996;5:513-24.
45. Ades A, Lu G, Claxton K. Expected value of sample information calculations in medical decision modeling. *Med Decis Making* 2004;24:207-27.

46. Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P. The role of modelling in prioritising and planning clinical trials. *Health Technol Assess* 2003;7:1-125.
47. Scott R, Ashton H, Kay D. Abdominal aortic aneurysm in 4237 screened patients: prevalence, development and management over 6 years. *Br J Surg* 1991;78:1122-5.
48. Vardulaki K, Prevost T, Walker N, Day N, Wilmink A, Quick C, et al. Growth rates and risk of rupture of abdominal aortic aneurysms. *Br J Surg* 1998;85:1674-80.
49. Bengtsson H, Bergqvist D. Ruptured abdominal aortic aneurysm: a population-based study. *J Vasc Surg* 1993;18:74-80.
50. Scott R, Wilson N, Ashton H, Kay D. Is surgery necessary for abdominal aortic aneurysm less than 6 cm in diameter? *Lancet* 1993;342:1395-6.
51. Ashton H, Buxton M, Day N, Kim L, Marteau T, Scott R, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet* 2002;360:1531-9.
52. Beard J. Screening for abdominal aortic aneurysm. *Br J Surg* 2003;90:515-6.
53. Earnshaw J, Shaw E, Whyman M, Poskitt K, Heather B. Screening for abdominal aortic aneurysms in men. *Bmj* 2004;328:1122-4.
54. Lindholt J, Juul S, Fasting H, Henneberg E. Screening for abdominal aortic aneurysms: single centre randomised controlled trial. *Bmj* 2005;330:750.
55. Scott R, Wilson N, Ashton H, Kay D. Influence of screening on the incidence of ruptured abdominal aortic aneurysm: 5-year results of a randomized controlled study. *Br J Surg* 1995;82:1066-70.
56. Norman P, Jamrozik K, Lawrence-Brown M, Le M, Spencer C, Tuohy R, et al. Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm. *Bmj* 2004;329:1259.
57. Lindholt J, Juul S, Fasting H, Henneberg E. Hospital costs and benefits of screening for abdominal aortic aneurysms. Results from a randomised population screening trial. *Eur J Vasc Endovasc Surg* 2002;23:55-60.
58. Multicentre aneurysm screening study (MASS): cost effectiveness analysis of screening for abdominal aortic aneurysms based on four year results from randomised controlled trial. *Bmj* 2002;325:1135.
59. Scott R, Vardulaki K, Walker N, Day N, Duffy S, Ashton H. The long-term benefits of a single scan for abdominal aortic aneurysm (AAA) at age 65. *Eur J Vasc Endovasc Surg* 2001;21:535-40.
60. SBU Alert. Screening for abdominal aortic aneurysm; 2003-12-17. Available at http://www.sbu.se/www/index.asp [Accessed June 2007].

61. Mehta S, Cannon C, Fox K, Wallentin L, Boden W, Spacek R, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *Jama* 2005;293:2908-17.
62. Fox K, Poole-Wilson P, Clayton T, Henderson R, Shaw T, Wheatley D, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005;366:914-20.
63. Kim J, Henderson R, Pocock S, Clayton T, Sculpher M, Fox K. Health-related quality of life after interventional or conservative strategy in patients with unstable angina or non-ST-segment elevation myocardial infarction: one-year results of the third Randomized Intervention Trial of unstable Angina (RITA-3). *J Am Coll Cardiol* 2005;45:221-8.
64. Epstein D, Sculpher M, Clayton T, Henderson R, Pocock S, Buxton M, et al. A strategy of early angiography compared to conservative management in non-ST-elevation myocardial infarction: cost results from the third randomised intervention treatment in angina (RITA-3) trial; *Accepted for publication in International Journal of Cardiology* 2007.
65. Bassand J, Hamm C, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. *Eur Heart J* 2007;28:1598-660.
66. Fox K, Steg P, Eagle K, Goodman S, Anderson F, Jr., Granger C, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *Jama* 2007;297:1892-900.
67. Rothwell P, Eliasziw M, Gutnikov S, Warlow C, Barnett H. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;363:915-24.
68. Nussbaum E, Heros R, Erickson D. Cost-effectiveness of carotid endarterectomy. *Neurosurgery* 1996;38:237-44.
69. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *Jama* 1995;273:1421-8.
70. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363:1491-502.

71. Cronenwett J, Birkmeyer J, Nackman G, Fillinger M, Bech F, Zwolak R, et al. Cost-effectiveness of carotid endarterectomy in asymptomatic patients. *J Vasc Surg* 1997;25:298-309.
72. Vascular Registry in Sweden - annual report 2006 [in Swedish]. Available at http://www.karlkirurgi.com/docs/swedvasc2006.pdf [Accessed May 2007].
73. Socialstyrelsen. *National guidelines for stroke care 2005 - support for priority setting*: Socialstyrelsen (National board of health and welfare): available at http://www.socialstyrelsen.se/Publicerat/2007/9577/2007-102-10.htm [Accessed June 20 2007].
74. Glick H, Polsky D, Schulman K. Trial-based economic evaluation: an overview of design and analysis. In: Drummond M, McGuire A, editors. Economic Evaluation in Health Care -Merging Theory with Practice. Oxford New York: Oxford University Press; 2001.
75. Sackett D, Straus S, Richardson W, Rosenberg W, Haynes R. *Evidence-Based Medicine -How to Practice and Teach EBM*. London: Churchill Livingstone; 2000.
76. O'Hagan A, Buck C, Daneshkhah A, Eiser R, Garthwaite P, Jenkinson D, et al. *Uncertain Judgements: eliciting experts' probabilities*. Chichester: John Wiley & Sons, Ltd; 2006.
77. Phillips C. The economics of 'more research is needed'. *Int J Epidemiol* 2001;30:771-6.
78. Crow P, Shaw E, Earnshaw J, Poskitt K, Whyman M, Heather B. A single normal ultrasonographic scan at age 65 years rules out significant aneurysm disease for life in men. *Br J Surg* 2001;88:941-4.
79. Lindholt J, Vammen S, Juul S, Henneberg E, Fasting H. The validity of ultrasonographic scanning as screening method for abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 1999;17:472-5.
80. Vazquez C, Sakalihasan N, D'Harcour J, Limet R. Routine ultrasound screening for abdominal aortic aneurysm among 65- and 75-year-old men in a city of 200,000 inhabitants. *Ann Vasc Surg* 1998;12:544-9.
81. Lederle F, Johnson G, Wilson S, Chute E, Hye R, Makaroun M, et al. The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med* 2000;160:1425-30.
82. Wilmink T, Quick C, Hubbard C, Day N. The influence of screening on the incidence of ruptured abdominal aortic aneurysms. *J Vasc Surg* 1999;30:203-8.
83. Lucarotti M, Shaw E, Heather B. Distribution of aortic diameter in a screened male population. *Br J Surg* 1992;79:641-2.

84. Smith F, Grimshaw G, Paterson I, Shearman C, Hamer J. Ultrasonographic screening for abdominal aortic aneurysm in an urban community. *Br J Surg* 1993;80:1406-9.
85. O'Kelly T, Heather B. General practice-based population screening for abdominal aortic aneurysms: a pilot study. *Br J Surg* 1989;76:479-80.
86. Simoni G, Pastorino C, Perrone R, Ardia A, Gianrossi R, Decian F, et al. Screening for abdominal aortic aneurysms and associated risk factors in a general population. *Eur J Vasc Endovasc Surg* 1995;10:207-10.
87. Boll A, Verbeek A, van de Lisdonk E, van der Vliet J. High prevalence of abdominal aortic aneurysm in a primary care screening programme. *Br J Surg* 1998;85:1090-4.
88. Holdsworth J. Screening for abdominal aortic aneurysm in Northumberland. *Br J Surg* 1994;81:710-2.
89. Bengtsson H, Bergqvist D, Ekberg O, Janzon L. A population based screening of abdominal aortic aneurysms (AAA). *Eur J Vasc Surg* 1991;5:53-7.
90. Bengtsson H, Sonesson B, Bergqvist D. Incidence and prevalence of abdominal aortic aneurysms, estimated by necropsy studies and population screening by ultrasound. *Ann N Y Acad Sci* 1996;800:1-24.
91. Bergqvist D, Troeng T, Elfstrom J, Hedberg B, Ljungstrom K, Norgren L, et al. Auditing surgical outcome: ten years with the Swedish Vascular Registry--Swedvasc. The Steering Committee of Swedvasc. *Eur J Surg Suppl* 1998:3-8.
92. Drott C, Arfvidsson B, Ortenwall P, Lundholm K. Age-standardized incidence of ruptured aortic aneurysm in a defined Swedish population between 1952 and 1988: mortality rate and operative results. *Br J Surg* 1992;79:175-9.
93. Brown L, Powell J. Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. *Ann Surg* 1999;230:289-96.
94. Statistics Sweden. *Statistical Yearbook of Sweden 2004*. Statistics Sweden: Örebro, 2003.
95. Johnston K. Nonruptured abdominal aortic aneurysm: six-year follow-up results from the multicenter prospective Canadian aneurysm study. Canadian Society for Vascular Surgery Aneurysm Study Group. *J Vasc Surg* 1994;20:163-70.
96. Vohra R, Reid D, Groome J, Abdool-Carrim A, Pollock J. Long-term survival in patients undergoing resection of abdominal aortic aneurysm. *Ann Vasc Surg* 1990;4:460-5.

97. Glimaker H, Holmberg L, Elvin A, Nybacka O, Almgren B, Bjorck C, et al. Natural history of patients with abdominal aortic aneurysm. *Eur J Vasc Surg* 1991;5:125-30.
98. Scott R, Tisi P, Ashton H, Allen D. Abdominal aortic aneurysm rupture rates: a 7-year follow-up of the entire abdominal aortic aneurysm population detected by screening. *J Vasc Surg* 1998;28:124-8.
99. Law M, Morris J, Wald N. Screening for abdominal aortic aneurysms. *J Med Screen* 1994;1:110-5.
100. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The UK Small Aneurysm Trial Participants. *Lancet* 1998;352:1649-55.
101. Lederle F, Wilson S, Johnson G, Reinke D, Littooy F, Acher C, et al. Immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 2002;346:1437-44.
102. Brown P, Zelt D, Sobolev B. The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. *J Vasc Surg* 2003;37:280-4.
103. Lederle F, Johnson G, Wilson S, Ballard DJ, Jordan W, Jr., Blebea J, et al. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. *Jama* 2002;287:2968-72.
104. Jones A, Cahill D, Gardham R. Outcome in patients with a large abdominal aortic aneurysm considered unfit for surgery. *Br J Surg* 1998;85:1382-4.
105. Bengtsson H, Nilsson P, Bergqvist D. Natural history of abdominal aortic aneurysm detected by screening. *Br J Surg* 1993;80:718-20.
106. Stonebridge P, Draper T, Kelman J, Howlett J, Allan P, Prescott R, et al. Growth rate of infrarenal aortic aneurysms. *Eur J Vasc Endovasc Surg* 1996;11:70-3.
107. Collin J, Heather B, Walton J. Growth rates of subclinical abdominal aortic aneurysms--implications for review and rescreening programmes. *Eur J Vasc Surg* 1991;5:141-4.
108. Santilli S, Littooy F, Cambria R, Rapp J, Tretinyak A, d'Audiffret A, et al. Expansion rates and outcomes for the 3.0-cm to the 3.9-cm infrarenal abdominal aortic aneurysm. *J Vasc Surg* 2002;35:666-71.
109. Wolf Y, Bernstein E. A current perspective on the natural history of abdominal aortic aneurysms. *Cardiovasc Surg* 1994;2:16-22.
110. Biancari F, Mosorin M, Anttila V, Satta J, Juvonen J, Juvonen T. Ten-year outcome of patients with very small abdominal aortic aneurysm. *Am J Surg* 2002;183:53-5.

111. Meltzer D. Accounting for future costs in medical cost-effectiveness analysis. *J Health Econ* 1997;16:33-64.
112. Bryan S, Buxton M, McKenna M, Ashton H, Scott A. Private costs associated with abdominal aortic aneurysm screening: the importance of private travel and time costs. *J Med Screen* 1995;2:62-6.
113. Carlsson P, Pedersen K, Varenhorst E. Costs and benefits of early detection of prostatic cancer. *Health Policy* 1990;16:241-53.
114. Ekman M, Zethraeus N, Jonsson B. Cost effectiveness of bisoprolol in the treatment of chronic congestive heart failure in Sweden: analysis using data from the Cardiac Insufficiency Bisoprolol Study II trial. *Pharmacoeconomics* 2001;19:901-16.
115. Burström K, Johannesson M, Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. *Qual Life Res* 2001;10:621-635.
116. Lindholt J, Vammen S, Fasting H, Henneberg E. Psychological consequences of screening for abdominal aortic aneurysm and conservative treatment of small abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2000;20:79-83.
117. Dolan P. Modeling valuations for EuroQol health states. *Medical Care* 1997;35:1095-108.
118. Hinterseher I, Saeger H, Koch R, Bloomenthal A, Ockert D, Bergert H. Quality of Life and Long-term Results After Ruptured Abdominal Aortic Aneurysm. *Eur J Vasc Endovasc Surg* 2004;28:262-9.
119. Joseph A, Fisher J, Toedter L, Balshi J, Granson M, Meir-Levi D. Ruptured abdominal aortic aneurysm and quality of life. *Vasc Endovascular Surg* 2002;36:65-70.
120. Korhonen S, Kantonen I, Pettila V, Keranen J, Salo J, Lepantalo M. Long-term survival and health-related quality of life of patients with ruptured abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2003;25:350-3.
121. Bohmer R, Fleischl J, Knight D. Quality of life after emergency abdominal aortic aneurysm repair. *Aust N Z J Surg* 1999;69:447-9.
122. Magee T, Scott D, Dunkley A, St Johnston J, Campbell W, Baird R, et al. Quality of life following surgery for abdominal aortic aneurysm. *Br J Surg* 1992;79:1014-6.
123. Hennessy A, Barry M, McGee H, O'Boyle C, Hayes D, Grace P. Quality of life following repair of ruptured and elective abdominal aortic aneurysms. *Eur J Surg* 1998;164:673-7.
124. Malina M, Nilsson M, Brunkwall J, Ivancev K, Resch T, Lindblad B. Quality of life before and after endovascular and open repair of asymptomatic AAAs: a prospective study. *J Endovasc Ther* 2000;7:372-9.

125. Prinssen M, Buskens E, Blankensteijn J. Quality of life endovascular and open AAA repair. Results of a randomised trial. *Eur J Vasc Endovasc Surg* 2004;27:121-7.
126. Perkins J, Magee T, Hands L, Collin J, Galland R, Morris P. Prospective evaluation of quality of life after conventional abdominal aortic aneurysm surgery. *Eur J Vasc Endovasc Surg* 1998;16:203-7.
127. Collet D. *Modelling survival data in medical research*. London: Chapman & Hall; 1994.
128. Government Actuary Department. Interim life tables. Expectation of life for males in the United Kingdom, based on data for the years 2002-2004. http://www.gad.gov.uk [Accessed October 21 2006].
129. National Statistics. *Review of the registrar general on deaths by cause, sex and age, in England and Wales.* London: National Statistics; 2003.
130. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53-72.
131. Spacek R, Widimsky P, Straka Z, Jiresova E, Dvorak J, Polasek R, et al. Value of first day angiography/angioplasty in evolving Non-ST segment elevation myocardial infarction: an open multicenter randomized trial. The VINO Study. *Eur Heart J* 2002;23:230-8.
132. Anderson H, Cannon C, Stone P, Williams D, McCabe C, Knatterud G, et al. One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial. A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave myocardial infarction. *J Am Coll Cardiol* 1995;26:1643-50.
133. Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 2006;368:998-1004.
134. de Winter R, Windhausen F, Cornel J, Dunselman P, Janus C, Bendermacher P, et al. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005;353:1095-104.
135. Boden W, O'Rourke R, Crawford M, Blaustein A, Deedwania P, Zoble R, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;338:1785-92.

136. McCullough P, O'Neill W, Graham M, Stomel R, Rogers F, David S, et al. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy. Results of the medicine versus angiography in thrombolytic exclusion (MATE) trial. *J Am Coll Cardiol* 1998;32:596-605.
137. Cannon C, Weintraub W, Demopoulos L, Vicari R, Frey M, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.
138. Greene W. *Econometric Analysis*. 5th ed. New York: Prentice Hall; 2003.
139. van Domburg R, van Miltenburg-van Zijl A, Veerhoek R, Simoons M. Unstable angina: good long-term outcome after a complicated early course. *J Am Coll Cardiol* 1998;31:1534-9.
140. Stinnett A, Paltiel A. Estimating CE Ratios under Second-order Uncertainty: The Mean Ratio versus the Ratio of Means. *Med Decis Making* 1997;17:483-489.
141. Kragsterman B, Parsson H, Lindback J, Bergqvist D, Bjorck M. Outcomes of carotid endarterectomy for asymptomatic stenosis in Sweden are improving: Results from a population-based registry. *J Vasc Surg* 2006;44:79-85.
142. Briggs A, Ades A, Price M. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. *Med Decis Making* 2003;23:341-50.
143. Ghatnekar O, Persson U, Glader E, Terent A. Cost of stroke in Sweden: an incidence estimate. *Int J Technol Assess Health Care* 2004;20:375-80.
144. Henriksson M, Lundgren F. Decision-analytical model with lifetime estimation of costs and health outcomes for one-time screening for abdominal aortic aneurysm in 65-year-old men. *Br J Surg* 2005;92:976-83 (Paper I).
145. Duncan P, Lai S, Keighley J. Defining post-stroke recovery: implications for design and interpretation of drug trials. *Neuropharmacology* 2000;39:835-41.
146. Haacke C, Althaus A, Spottke A, Siebert U, Back T, Dodel R. Long-term outcome after stroke: evaluating health-related quality of life using utility measurements. *Stroke* 2006;37:193-8.