The matter of economic evaluations in health policy decision-making

The case of the Swedish national guidelines for heart diseases

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´The time has come,´ the Walrus said
L. Carroll

CONTENTS

ABSTRACT

Economic evaluations are used to inform decision makers about the efficient allocation of scarce healthcare resources and are generated with the direct intent to support decisions in healthcare. Producing guidelines is a complex process and the inclusion of health-economic aspects in the formulation of the Swedish national guidelines as a basis for the written recommendations (priority gradings), distinguishes them from their European counterparts. Despite the increased use of cost-effectiveness data in decision-making, little is known about the actual use of such data. This thesis covers issues concerning how economic evaluations matter in health policy decision-making. The thesis includes four papers based on the Swedish national guidelines for heart diseases, one of the most prominent examples in Sweden of following the notion of evidence-based policy (EBP), in order to inform explicit priority setting.

Both Papers I and II followed a qualitative case study design, based on the same data set. Paper I explored how a specific working group, the Priority Setting Group (PSG), handled the various forms of evidence and values when producing the national guidelines. Two themes were identified in reaching collective agreement in priority gradings; group facilitation activities and avoiding deadlock in the discussion. The work process involved disagreement and negotiation as part of that task. Paper I contributes to the theoretical and practical debate on EBP. Paper II focused on the use of cost-effectiveness data as decision support in the PSG work process. The paper addressed availability of cost-effectiveness data, evidence understanding, interpretation difficulties, and the reliance on evidence. Three themes were identified. The paper contributes to knowledge on how cost-effectiveness evidence was used in actual decision-making. The use of cost-effectiveness evidence was one of many tools employed to avoid deadlock in discussion and to reach a priority grading, when the overall evidence base was weak, in times of uncertainty and on the introduction of new expensive medical technologies.

Quantitative research methods were used for both Papers III and IV. Paper III explored how the PSG was presented with cost-effectiveness evidence as decision support and as a basis for their priority gradings. Cost-effectiveness ratios (ICERs) were provided, based on a systematic literature review, as well as how the results may be conveyed and communicated, for the treatment of

heart diseases using a cost-effectiveness ranking or league and providing valid information within a limited space, aiding decision makers on the allocation of healthcare resources. The thesis also includes decision support in the form of cost-effectiveness analysis on catheter ablation treatment. Paper IV provides an example of presenting evidence in the form of a decision-analytic model. The modelling approach provides an analytic framework for decision-making, specifically under conditions of uncertainty as in the introduction of new medical technology. Catheter ablation was associated with reduced cost and an incremental gain in quality adjusted life years (QALYs), and was considered a cost-effective treatment strategy compared to the medical treatment strategy in a lifetime perspective.

LIST OF PAPERS

I.   Nathalie Eckard, Ann-Charlotte Nedlund, Magnus Janzon and Lars-Åke Levin. Reaching agreement in uncertain circumstances: The practice of evidence-based policy in the case of the Swedish National Guidelines. *(Submitted)*

II. Nathalie Eckard, Magnus Janzon and Lars-Åke Levin. Use of cost-effectiveness data in priority setting decisions: Experiences from the national guidelines for heart diseases in Sweden. *International Journal of Health Policy and Management*, 2014, 3, 323-332.

III. Nathalie Eckard, Magnus Janzon and Lars-Åke Levin. Compilation of cost-effectiveness evidence for different heart conditions and treatment strategies. *Scandinavian Cardiovascular Journal*, 2011, 45, 72-76.

IV. Nathalie Eckard, Thomas Davidson, Håkan Walfridsson and Lars-Åke Levin. Cost-effectiveness of catheter ablation treatment for patients with symptomatic atrial fibrillation, *Journal of Atrial Fibrillation*, 2009, 1, 461-470.

ABBREVIATIONS

AAD Antiarrhythmic drug treatment
ACC The American College of Cardiology
AF Atrial fibrillation
AHA The American Heart Association
CAD Coronary artery disease
CBA Cost benefit analysis
CEA Cost-effectiveness analysis
CMA Cost minimisation analysis
CUA Cost-utility analysis
CVD Cardiovascular disease
ESC The European Society of Cardiology
EBM Evidence-based medicine
EBP Evidence-based policy
ICD Implantable cardioverter defibrillator
ICER Incremental cost-effectiveness ratio
LY Life year
NICE The National Institute for Health and Care Excellence
NBHW The National Board of Health and Welfare
PCI Percutaneous coronary intervention
PO Prioritisation object
PSG Priority setting group
QALY Quality adjusted life year
QoL Quality of life
RFA Radiofrequency catheter ablation
SEK Swedish kronor (currency)
SBU The Swedish Council for Health Technology Assessment.
TLV The Dental and Pharmaceutical Benefits Agency

INTRODUCTION

Background

Very little is known about decision-makers´ attitudes to these issues and the ways in which economic results of economic studies, however performed, are used in decision-making. This is likely to be a priority for research in the future [1] p.359.

These concluding remarks in the final chapter of *Methods for the Economic Evaluation of Health Care Programmes*, a well-known book to most health economist researchers, was the point of departure for my own research [1]. The final chapter discusses a range of issues relating to the presentation and use of economic evaluations, including cost-effectiveness ranking or league tables.

The objective of all economic evaluations is to improve decisions and inform decision makers about the efficient allocation of scarce healthcare resources. Economic evaluations provide a means of translating relevant evidence of both cost and effects of alternative treatment strategies being compared. Though decisions are not purely based on economic considerations, they may be incorporated in the decision-making process in order to make efficient decisions. They are generated with the direct intent to support decisions in healthcare. In Sweden, the national level authorities include the National Board of Health and Welfare (NBHW), which incorporates economic evaluations when producing national guidelines for priority setting, The Dental and Pharmaceutical Benefits Agency (TLV) in their process for reimbursement of pharmaceuticals, and the Swedish Council for Health Technology Assessment (SBU). The Swedish national guidelines include cost-effectiveness data in as basis for their recommendations or priority gradings and economic evaluations are an integrated part of the evidence base [2]. My own research interest and focus is on the importance of the results of economic evaluations and their use in health policy decision-making.

Economic evaluations have been increasingly used in decision-making, and despite the large production of cost-effectiveness data, little is known about the actual use of such data. Empirical studies have shown that cost-effectiveness analysis (CEAs), by themselves, have limited impact on decision makers [3, 4], which has raised concerns [5, 6]. Acceptability and acceptability barriers are often mentioned as of the limited impact of economic evaluations in decision-

making [4, 7]. The difficulties decision makers face in obtaining economic evaluations have been highlighted, due to shortage of relevant analyses or problems accessing those published [3]. Institutional barriers have also been mentioned as the cause of limited impact [8], specifically in local-level decision-making [3, 9]. One reason for the lack of acceptance at local level is affordability is often a pressing issue. Outcomes (effects) are seldom viewed in relation to costs, i.e. clinicians are often concerned with clinical effectiveness. Managers are often concerned with reducing costs, i.e. length of stay in hospital and expensive equipment. Neither view relates to both costs and effects. Local-level decision-makers often have no incentives to promote the status of economic evaluations, as opposed to at a national policy level in Sweden, where a societal perspective, including both costs and effects is often applied. Thus, there is a need for more research in this field.

The Swedish national guidelines

Many countries, including Sweden, have agencies that are following the notion of evidence based policy (EBP) in order to inform explicit priority setting. Examples of areas are drug approval, reimbursement systems and the use of cost-effectiveness studies in recommendations and guideline documents mentioned above. The most prominent example in Sweden, and also the focus of this thesis, is the national guidelines, produced by the NBHW, which has been influenced by the work of the National Institute for Health and Care Excellence (NICE) in the UK [10-12]. The NBHW, a government agency in Sweden under the Ministry of Health and Social Affairs, is responsible for producing the national guidelines. The guidelines represent a policy instrument that systematically incorporates research evidence into policies. An important aspect of the guidelines is that they should be based on current scientific research to ensure that the decisions are offered on equal terms, and the patients receive medical care according to their needs so that they may attain maximum benefits. Further more, clinical, economic and ethical considerations also influence the decisions.

A key notion in producing guidelines is that greater reliance should be placed on scientific evidence for deriving policy decisions systematically. The idea that clinical practice should be based on "best" evidence follows the evidence-based medicine movement (EBM), a term first coined in the 1990s, which was when the gap between research and practice became apparent. Thus, the process of

developing guidelines involves systematic collection and compilation of high-quality evidence on treatments to support decision-making. It is important to ensure that clinical guidelines are consistent with scientific evidence and clinical judgement in order to produce valid guidelines [13].

The resources of society are scarce. Therefore, decision makers and politicians must prioritise the allocation of these resources. The Swedish national guidelines have been provided to support the decisions on the efficient allocation of scarce healthcare resources. They should support explicit priority setting in healthcare, letting ethical considerations influence the recommendations. The Swedish approach to priority setting is based on the ethics platform for making priority setting decisions in healthcare and regulated by law [14]. These principles are provided below in a hierarchical order:

Human dignity principle: All individuals have equal value and rights regardless of their personal characteristics and social position.

Needs and solidarity principle: Healthcare resources should be allocated according to need.

Cost-effectiveness principle: Resources should be used in the most effective way without neglecting fundamental duties to improve health and quality of life (QoL) (aimed at a reasonable relation between cost and effect) [15].

A model to operationalize the contents of the three ethical principles is used by the NBHW when producing national guidelines for priority setting [16] (Table 1).

The goal of the national guidelines is to ensure that the patients receive high-quality medical care. According to Swedish law, healthcare should be offered on equal terms, effective, evidence-based, patient-focused and secure [14]. The guidelines for heart diseases were amongst the first to be published in 2004. They was substantially revised in 2008 and have been updated since. Today, guidelines for nine different disease areas have been produced by the NBHW including, besides heart diseases, stroke care, care in cases of depression and anxiety disorders, diabetes care, lung cancer care and treatment, and musculoskeletal diseases. One criterion used by the NBHW for choosing the disease areas is that the disease area should cover a large group of patients with serious chronic illness, that makes a claim on society´s resources. One such disease area is cardiovascular disease (CVD).

Priority setting in guidelines

Once the NBHW have decided to work on a new guideline, qualified experts are tied to the areas concerned. Expert groups are responsible for conducting systematic literature searches, reviewing and compiling the current available scientific knowledge to produce decision support. Involved in the production of the national guidelines for heart diseases were medical and health-economic groups of experts and the Priority Setting Group (PSG). The project management together with the experts propose pairs of medical conditions and interventions, henceforth denoted as the prioritization objects (POs). The POs were chosen to give guidance in a specific situation in clinical practice where the need for guidance is the greatest, and should be focused on typical cases, representing large volumes as well as controversial areas where there are differences in praxis as well as in cases of new expensive treatments or uncertainty. The literature findings on evidence of the severity of the condition, the patient benefit-risk, and cost-effectiveness are compiled and presented in both short text descriptions and table formats for each PO [17]. This work was undertaken prior to the PSG beginning their work process in preparing their priority grading.

Table 1. Components considered in priority gradings [16].

Human dignity principle			
Needs and solidarity principle		**Cost-effectiveness principle**	
Severity of the condition	**Patient benefit/ Effect of intervention**	**Cost-effectiveness of the intervention**	
*Health condition - suffering - functional impairment - quality of life	*Effects on health condition - suffering - functional impairment - quality of life	*Direct costs - interventions - other measures (for example travel)	E V I
*Risk of - premature death - disability/continued suffering - impact on quality of life	*Effects on risk of - premature death - disability/continued suffering - impact on quality of life	*Indirect costs	D E N
	*Risk of side effects (adverse events) or serious complications from the intervention	*…in relation to patient benefit*	C E

The information compiled by the groups of experts was used by the PSG as decision support when producing priority gradings.

The PSG work process involves being informed on every PO and appraising the evidence provided by the groups of experts. A consensus process was used to grade each PO on a scale ranging from 1 to 10, with 1 denoting the highest priority intervention and 10 denoting the lowest. Certain medical conditions could be given higher priority gradings, i.e. given more resources than others, depending on the seriousness of the medical condition. In general, a low ranking reflects uncertainty in the effect of the treatment or insufficient scientific data, often at high cost [18]. Therefore, cost-effectiveness evidence may be viewed as part of the evidence-based knowledge used for decision-making. Ethical considerations were also incorporated in the priority gradings. In addition, the NBHW tried to focus on POs where there is a significant need for guidance on the part of decision-makers and the professionals concerned.

Clinical guidelines – international perspective

Cardiovascular disease

CVD is the leading cause of death around the world [19]. It places a substantial burden on healthcare systems. CVD mortality rates have improved in the major part of western and northern Europe during the last three decades. Improvements in CVD mortality rates are due to reduced incidence, i.e. primary prevention and risk factor management. CVD also contributes to morbidity, using indicators such as hospital discharge rates, prevalence, and incidence rates. CVD can be reduced with improvements in treatment and care, as well as policies that focus on reducing risk factors such as smoking associated with CVD.

While there is a trend towards declining mortality from CVD in developed countries, projections suggest that it will still be the leading cause of death globally in 2030 [20]. This is largely because population growth and population ageing are likely to increase the coronary artery disease (CAD) mortality rate, offsetting the benefits achieved by improved treatments and reductions in risk factors. Many risk factors for CAD, particularly obesity, have been increasing substantially over a period. Therefore, the morbidity and socioeconomic burden of CAD, which is considerable, will continue to have a major impact over the coming decades.

Clinical guidelines

The European Society of Cardiology (ESC) is assigned to producing clinical guidelines for heart diseases in Europe. The ESC is an independent association of national societies of cardiology from all European countries, though funding is also sponsored by the pharmaceutical and medical device industry. Economic aspects are not dealt with in the European setting [2]. There are no comparisons of new versus old treatment strategies in terms of costs and QALYs gained. Consequently, there is no corresponding process or need to prioritise or chose between different healthcare interventions. In the European setting, the task force specialists provide consensus decisions reflecting the effectiveness of the method used in clinical practice. The European guidelines review medical treatments for different conditions.

The American College of Cardiology (ACC) and the American Heart Association (AHA) have a shared responsibility to provide recommendations

applicable to patients at risk of developing CVD. The focus is on medical practice in the United States. The ACC/AHA often develop practice guidelines in conjunction with each other, translating scientific evidence into clinical practice guidelines, for example guidelines for the clinical management of atrial fibrillation (AF) [21]. The ACC/AHA guidelines are developed similarly to the European guidelines, focusing on the medical needs of the patient and the appropriate healthcare for specific clinical circumstances. The clinical guidelines are systematically developed to assist practitioners in patient decisions and are published in separate fields of heart disease.

Health policy decision-making

In examining health policy decision-making and public health policy processes, the use of an analytical framework may assist in understanding aspects in policymaking. According to the public policy cycle or heuristic stage models (see for example [22-25]) the process of producing public policies can be divided into several stages, the numbers of stages varying between five and seven. A common five model stages offers a framework for the generic features of policy decision-making 1) agenda setting, i.e. the process through which policy and the problem is intended to be addressed and placed on the agenda 2) policy formulation, i.e. determining in which direction the policy will take place, setting objectives, considering policy options and possible solutions 3) adoption or decision-making, i.e. the stage in which decisions are made at the government level, that favours one or more approaches to addressing a given problem 4) implementation, i.e. determining the actual effect of a policy and how well it achieves its objectives, effecting the outcome of the policy 5) evaluation, i.e. the stage during which policy is evaluated to verify whether its implementation and effects are aligned with the objectives that were explicitly or implicitly set out [26].

The model provides a framework for reflecting on the processes surrounding development of public policy. The stages model separates out the different activities associated with public policy. However, developing public policy is not a linear process. The emphasis in the stages model cycles highlight policymaking as fluid. By reflecting on the stage at which for example public health actors can better determine the purpose and the type of information required. Implementation studies have often made use of the stages model to position implementation within the policy cycle [27] and difficulties in

implementing policies [28, 29]. Though, the focus of this thesis is in the adoption or decision-making stage. The model offers schematic simplification of a rather complex world of public policy.

Public health actors are thus involved in producing policy documents to guide explicit priority setting in healthcare. The Swedish national guidelines represents a policy instrument that systematically incorporated research evidence, both clinical and economic evidence, in policymaking in the adoption or decision-making stage. The negotiations where policymakers exchange information, rework interpretations and give meaning to different policy matters, as in this case the "best" evidence for the treatment of heart diseases, can be understood as a way to find support in an ambiguous situation of formulating recommendations in the form of guidelines. The work in producing guidelines is not easily achieved, in practice the work involve negotiations and collective sense making [29, 30].

The work with policies is also highly routinized where various organizational routines constrain how negotiations can be conducted [29]. However, in the face of complexity and ambiguity, these constraints enable policymakers to act by reducing options [31]. A substantial part of policy decision-making takes place, not only in negotiating with others, but also in writing documents, trying to find a mutually acceptable outcome that is related to the broader framework of meaning in which they are located. Thus, negotiations take place in these "mediating institutions" [29], and their document writing specifically concerns that there is that some sort of "input" is transformed into something other. Policy documents, such as the Swedish national guidelines, illustrate that decisions due to uncertainty and potentially conflictual evidence, need to be interpreted and negotiated, and interpreted again by those who use guidelines [32].

Economic evaluations are used as tool to inform decision makers as decision support in the decision-making stage of the policy cycle model. One framework which is commonly mentioned to explain the conditions that need to be fulfilled to enable use of cost-effectiveness data are the categories, accessibility and acceptability. The term accessibility refers to the availability of relevant evidence delivered in a timely manner and the extent to which the evidence can be understood by the decision makers for example, decision makers often struggle with understanding health economic analyses given the concepts, language and presentation style [3, 4]. The term acceptability refers to

interpretation (concepts and language, presentational style, attitudes, perceptions, and reliance on the evidence) [4]. Acceptability barriers refer to all barriers that arise after economic evaluations have been accessed and understood, such as; scientific acceptability and institutional barriers (especially mentioned as a barrier in local decision making) [3, 9]. Certain conditions need to be fulfilled to enable the use of cost-effectiveness data in real life [9]. These conditions include; lack of budget restriction, strategies to handle uncertainty, transparency, legitimising health economics and the clear instructions (use of templates) [9]. Institutional considerations associated with incentives to employ economic evaluations include; stated aims and goals, relationship to implementation, institutional affiliation of actors and external scrutiny levels [8].

Economic evaluations

Analytical approaches to economic evaluations

Economic evaluations are used to inform decision makers about the efficient allocation of scarce healthcare resources. All forms of economic evaluations compare costs and consequences of an intervention with a relative alternative. There are four main forms of economic evaluations, as described in Table 2. They differ in the way the health consequences of health programmes are measured and valued.

Table 2. The main forms of measurement of costs and consequences in economic evaluations.

Type of evaluation	Measurement/ Valuation of costs	Measurement/ Valuation of consequences
Cost minimisation analysis (CMA)	Monetary units	Not measured (assumption the effects of alternatives are identical)
Cost-effectiveness analysis (CEA)	Monetary units	Natural units (for example life years gained or avoided event)
Cost-utility analysis (CUA)	Monetary units	Quality adjusted life years (QALYs)
Cost benefit analysis (CBA)	Monetary units	Monetary benefit

The first form of economic evaluation is the *cost minimisation analysis* or *cost analysis*, which deals with costs only. This type of analysis can be used when the effects or consequences of the compared treatments/ healthcare programmes are considered equivalent. The treatment with the lowest cost is considered cost-effective.

In a c*ost-effectiveness analysis (CEA)*, the consequences of programmes are valued as, for example, event avoided and life year (LY) gained. However, one of its setbacks is that treatments can affect patients in different ways. One treatment may be associated with survival benefits and another treatment with QoL improvements. It is also difficult to compare different programmes with each other when different effect measures are used.

Cost-utility analysis (CUA) is the most common form of health-economic evaluation. It is similar to the CEA but uses QALY as an outcome measure.

In the *cost benefit analysis (CBA)*, attempts are made to value the consequences of programmes in monetary terms. Both costs and effects of the compared treatment strategies are measured in monetary units. CBA is not commonly used in the healthcare sector due to the practical difficulties involved in the valuation of health effects in monetary units.

CEA and decision-analytic modelling

As presented earlier, CEA is a common form of evaluation in healthcare decision-making. Both costs and effects are considered in the CEA, including a comparison of the value for money of alternative treatment strategies for a particular patient group.

The CEA provides a means of translating relevant evidence into estimates of costs and effects. In the absence of long-term data, a decision-analytic modelling approach can be used to estimate costs and effects over an appropriate time horizon, often beyond the follow-up of clinical trials. A synthesis of the best available evidence may be used, drawing on evidence from data sources where input variables may readily be changed for alternative scenarios.

QALY is the most commonly used outcome measure for health. The QALY combines LY with the value of health states during these LY. One QALY reflects living one year in full health. Cost-effectiveness results are often calculated in terms of cost per QALY or LY gained for one treatment strategy compared to another.

The results presented as incremental cost-effectiveness ratios (ICERs), i.e. the ratio of the difference in health outcome (QALYs) between two alternatives: treatment A and treatment B. The results are measured in terms of additional (incremental) costs and QALYs gained (incremental effects). Thus, the ICER shows the mean incremental cost of gaining an extra QALY by employing the treatment A strategy compared to the treatment B strategy. A low ICER indicates greater cost-effectiveness compared to a higher ICER value.

$$ICER = (Cost\ A - Cost\ B) / (Effect\ A - Effect\ B)$$

The results of a CEA may also be illustrated in a cost-effectiveness plane (Figure 1). The horizontal axis represents the incremental effects, i.e. difference in effects of the evaluated treatment strategy and its comparator. The vertical axis represents the incremental costs. An ICER situated in the south east quadrant would thus imply a dominant treatment strategy, i.e. more effective and less costly than the alternative treatment strategy. If the ICER is situated in the north east quadrant, the treatment strategy is more effective but costs more than its

comparator. Whether the treatment is considered to be cost-effective depends on the acceptance curve or threshold value representing society´s willingness to pay for the effect, for example QALY.

Cost difference
+

Intervention less effective
and more costly than comparator

Intervention more effective
and more costly than comparator

-   + Effect
difference

Intervention less effective
and less costly than comparator

Intervention more effective
and less costly than comparator
(dominant)

-
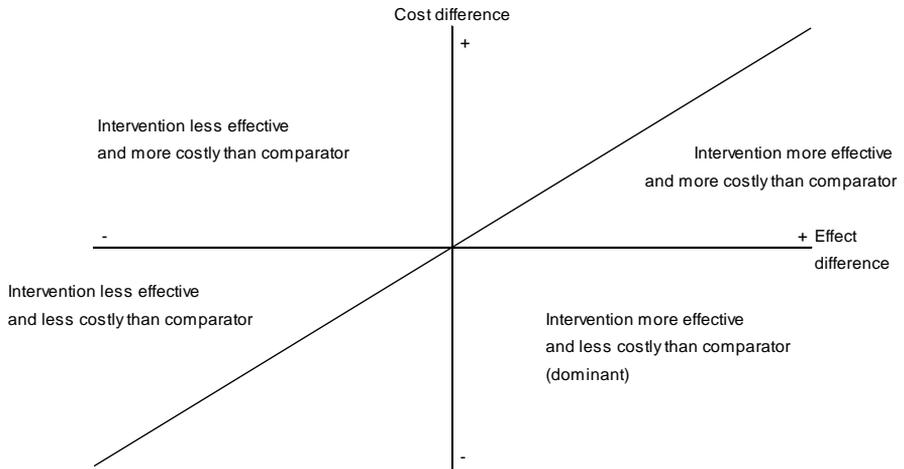
Figure 1. The cost-effectiveness plane.

Ranking or league tables

Cost-effectiveness ranking or league tables provide a means of presenting cost-effectiveness evidence in terms of cost per QALY or LY gained. Using a generic outcome measure, such as QALYs, enables comparisons across different cost-effectiveness analyses. League tables have been published both in North America and the United Kingdom [33, 34]. An extensive list of over five hundred ICERs for life-saving interventions, including interventions for heart diseases, has also been presented by Tengs [35].

There are many methodological issues of importance when interpreting cost-effectiveness rankings and comparing ICERs. The accuracy of the results presented in a cost-effectiveness ranking or league table is always limited by the accuracy of data and assumptions upon which the original analysis was based.

These assumptions include the range of cost and consequences considered, the method for estimating utility values for health states, the discount rate used and the choice of comparator [36]. Whether a programme is cost-effective depends on what we compare it to. The choice of comparison programmes is probably most important for the interpretation of ICERs [36-38]. They are to a large extent context-specific [39]. Transferring results from one setting to the other (demography, availability of healthcare resources, relative prices etc.) may constitute a problem as different countries have different health systems and different perspectives, for example use different discount rates [40].

Another aspect of cost-effectiveness ranking or league tables is that they often use point-estimates giving a false sense of precision and rarely include measures of uncertainty for these estimates [40]. An alternative methodological approach would be to provide information on mean values as well as variance. Another way would be to use a graphical framework, such as the cost-effectiveness plane, to present results [41]. A scatterplot diagram is a simple solution to illustrate the uncertainty in the results of cost-effectiveness analyses. Stochastic rankings have also been proposed for use in a budgetary context [42-45].

However, in the absence of systematic comparisons such as cost-effectiveness rankings, comparisons between healthcare programmes are likely to take place informally [46]. Assembling data on a range of interventions gives greater prominence to cost-effectiveness data than does the reporting of cost-effectiveness studies individually [36-38]. The type of evidence included in a cost-effectiveness ranking or league table is a condensed form of information. It constitutes a quality assessment and structured summary of economic evaluations, and may be used as a guide to navigating within the field of heart diseases and economic evaluations. This compilation of ICERs may also be used to identify areas that lack cost-effectiveness analyses.

Outline of thesis

The thesis is structured as follows: Chapter 1 includes an overview of the analytical framework used in the thesis including a brief introduction of basic concepts, presentation of the case study, theoretical perspectives on health policy decision-making and analytical approaches to economic evaluations. Chapters 2 and 3 provide the aims of the thesis and the material and methods used including ethical considerations. Chapter 4 provides the results of the four

included papers. Paper I highlights the process and the practice of producing national guidelines. Paper II sheds light on issues encountered when interpreting cost-effectiveness data used in priority gradings. Paper III presents ICERs, based on an extensive systematic literature search, for the treatment of different heart diseases as well an exploration of how the results may be conveyed and communicated in the so-called cost-effectiveness ranking or league tables, and used as decision support. In Paper IV a decision-analytic modelling approach was used to assess the cost-effectiveness for a new medical technology. Chapter 5 comprises a discussion of methodological considerations and the results of the study, and conclusions. Due to the limited space available in journal papers, the detailed description of used methods are found in Chapter 3 and additional information are found in the enclosed appendices for the interested reader.

AIMS OF THE THESIS

Overall aim

The overall aim of this thesis was to explore how economic evaluations matter in health policy decision-making, and how they are understood and used by decision makers. This was covered in four papers. All four papers are based on the Swedish national guidelines for heart diseases.

Specific aims

- To explore the practice of evidence-based policy (EBP) in a national healthcare context, i.e. how decision makers handle various forms of evidence and values, and how they make sense of, and come to agreement on, recommendations that constitute the national guidelines.

- To investigate how a decision-making group used cost-effectiveness data in priority setting decisions in the case study of Swedish national guidelines for heart diseases.

- To present a compilation of cost-effectiveness ratios in ranking or league tables for the treatment of heart diseases based on an extensive systematic literature search. Further, to explore how the results may be conveyed and communicated to decision makers.

- To assess the cost-effectiveness of a new medical technology, catheter ablation (RFA), compared to antiarrhythmic medical treatment (AAD) for patients with symptomatic AF not previously responding to AAD.

MATERIALS AND METHODS

Preconceptions as a researcher

The choice of methods will be affected by a researcher´s epistemological orientation and his or her views on different methods for investigating the central phenomena under study [47]. A researcher´s background and position will also affect what he or she chooses to investigate. The preconceptions of a researcher thus affect the angle of the investigation, the choice of appropriate methods, the consideration of findings and communication of the conclusions [48]. However, it is important to point out that preconceptions are not the same as bias, unless the researcher fails to mention them of course [48].

Early on in my research career, I was part of a health-economic expert group involved in reviewing and compiling available scientific knowledge on cost-effectiveness as decision support for the national guidelines for heart diseases. During the course of the work, it became apparent to me that, despite the increasing demand and output of economic evaluations and cost-effectiveness analyses, very little was known about their actual use. I was curious to find out how economic evaluations are presented, communicated, interpreted and used by the intended audience – the healthcare decision makers. A preconception thus involved me in the role of a health economist with a special interest in the use of cost-effectiveness data in decision-making.

However, qualitative research methods are seldom used in the field of health economics. For this research project the observations were made prior to interviewing. Thus I had already observed the decision-making process when designing the questions in the interview guide. The observations gave me preconceptions on the decision-making process and I pursued the analysis through interviewing. Being familiar with the PSG members and their work process prior to interview, provided both preconceptions as well as access to individual members. I was aware of my responsibility to reflect the group as a whole, and did not speak to individual members more than necessary during the PSG meetings. Further ethical considerations are found at the end of this chapter.

Mixed methods approach as research design

Rather than thinking of qualitative and quantitative research as incompatible, they should be seen as complementary [48] p.483

It has been argued that mixed methods research, where quantitative and qualitative methods are combined, can be particularly useful in healthcare research because of the complexity of the phenomena studied [49]. Traditionally, quantitative research methods are used in the field of health economics, to present and compile information on cost-effectiveness often provided as decision support. However, I wanted to explore the decision-making process, i.e. the context in which decisions takes place as well as the use of cost-effectiveness, not only how it is presented, but how it is communicated, interpreted and used by decision makers. Therefore, due to my own research interests, I believed that using both quantitative and qualitative research methods would be useful in approaching the research questions I was interested in exploring. A mixed methods approach seemed appropriate in this thesis in order to explore the research of interest. In this thesis I have chosen to answer my research questions by using different methods for the analyses, and also to generate data in the collected data material. Papers III and IV are examples of quantitative methods, i.e. how to compile, present and convey information on cost-effectiveness provided as decision support to decision makers. The results are based on literature searches and decision-analytic modelling using several sources of data as input parameters. Papers I and II, on the other hand, focus on how decision-support may be communicated, interpreted and used by decision makers, i.e. using qualitative research methods. The thesis as a whole may therefore be seen as a case of mixed methods to study the matter of use and presentation of economic evaluations in healthcare decision-making.

Broadly defined, mixed method refers to research in which the researcher collects and analyses data, and integrates the findings, using both quantitative and qualitative approaches. Characteristics of true mixed methods involve the integration of both collection and data analyses of data sets using the two different methods. Mixed methods may also refer to data collection carried out separately and findings not compared until the interpretation stage. Thus, using more than one qualitative method to carry out an investigation may also be referred to as a mixed method approach, since each method brings a particular kind of insight to the study [47]. As with all decisions about the choice of methods, the objective of the study and the nature of the data required to meet

these objectives, will be central to the use of two or more qualitative methods. These issues also need to be reflected upon during the whole process.

Qualitative and quantitative research methods are different tools for answering different research questions. The role of the evidence-based practice movement in medical research and its relation to legitimacy of qualitative research is important to understand [50]. Evidence-based practice is commonly regarded as adequate for the biomedical research for which it was developed, but it is commonly argued that it is not useful when extrapolated to other forms of qualitative research. Questionnaires and interview, following mechanically standard rules with minimum personal judgement, are not compatible with qualitative interviews that rest upon the researcher´s skills and personal judgment in posing the questions. The explorative, interactive, and case-based approaches of many qualitative studies clashed with the logic of strictly controlled experimentation [50]. Hence, the quotation at the beginning of this section, where Malterud emphasizes the value of seeing qualitative and quantitative methods as complementary [48].

Papers I and II involve the use of both observations and in-depth interview as research methods. The benefits of using both observations and interviews as data sources are that they may be brought together to verify validation of data through triangulation, comparing interview data with data from observations. To observe all PSG meetings gave insight into the entire work process. Thus the interviews supplemented the findings from the observations. Both Papers I and II are based on a single case study where qualitative research methods were used. Paper I highlights the process and the practice of producing national guidelines. Paper II sheds light on issues encountered when interpreting cost-effectiveness data used in priority gradings, and also gives examples of if and when cost-effectiveness evidence made an impact on priority setting for the national guidelines.

Paper III presents ICERs, based on an extensive systematic literature search, for the treatment of different heart diseases as used in the national guidelines, as well as an exploration of how the results may be conveyed and communicated in the so-called cost-effectiveness ranking or league tables, and used as decision support. In Paper IV a decision-analytic modelling approach was used to assess the cost-effectiveness for a new medical technology (catheter ablation), with limited clinical evidence, for the treatment of AF. An overview of materials and methods are provided for in Table 3.

Table 3. Overview of the materials and methods used in the four included papers.

	PAPER I	PAPER II	PAPER III	PAPER IV
Title	Reaching agreement in uncertain circumstances: The practice of evidence-based policy in the case of the Swedish National Guidelines	Use of cost-effectiveness data in priority setting decisions: Experiences from the national guidelines for heart diseases in Sweden	Compilation of cost-effectiveness evidence for different heart conditions and treatment strategies	Cost-effectiveness of catheter ablation treatment for patients with symptomatic atrial fibrillation
Overall study aim	To explore the practice of evidence-based policy (EBP) in a national healthcare context, i.e. how decision makers handle various forms of evidence and values, and how they make sense and come to agreement on recommendations that constitute the national guidelines	To investigate how a decision-making group used cost-effectiveness data in priority setting decisions in a case study of Swedish national guidelines for heart diseases	To present a compilation of cost-effectiveness ratios for the treatment of heart diseases and to explore how the results may be conveyed and communicated, based on an extensive systematic literature search.	To assess the cost-effectiveness of a new medical technology, catheter ablation, compared to antiarrhythmic medical treatment, for patients with symptomatic atrial fibrillation (AF)
Data material	Observations In-depth interviews	Observations In-depth interviews	Systematic literature search	Several sources
Approach	Qualitative	Qualitative	Quantitative	Quantitative
Data analysis/ results	Thematic analysis	Thematic analysis	Compilation of results in a cost-effectiveness ranking or league table	Cost-effectiveness analysis using decision analytic modelling approach

Papers I-II

Observations and in-depth interviewing

Both Papers I and II followed a qualitative case study research design and are based on the same data set. Therefore, in this section I have chosen to present what the two papers have in common as well as the differences in analyses. Paper I focused on the process and practice of producing national guidelines, based on both clinical and economic evidence within the cardiovascular field, and Paper II focused on the use of cost-effectiveness data as decision support in the PSG work process. The national guidelines was chosen as a case study because it is one of the most prominent examples in Sweden, of a policy document following the notion of EBP in order to inform explicit priority setting. The work process includes systematically incorporating research evidence, both clinical and health economic, in decision-making. It is the PSG, i.e. the decision makers who are involved in the production of the guideline document. Thus, the work process of the members of the PSG involves being informed on the underlying evidence as decision support, and appraising the evidence. I could have chosen other stages of the work process in the production of the guidelines, though it is the PSG who are involved in the actual decision-making process, not the expert groups who provide decision support to the PSG. However, an exploratory approach was chosen in order to study the process and practice of producing the national guidelines to study the phenomena of actual negotiations during the course of the work process. The phenomena of reaching collective agreement through negotiations could not have been studied without access to the PSG.

The PSG was made up of twenty-one experts from the clinical field including a health economist and an ethicist. Physicians were in the majority, for example cardiologists, thoracic surgeons and clinical physiologists. Other stakeholders such as general practitioners, nurses and physiotherapists were also represented. The idea behind this was that the PSG should have a multi-professional composition, have trust within its own profession as well as a fair geographical distribution. Thus, I had the opportunity of being able to follow the process of producing, compiling and presenting the underlying evidence (cost-effectiveness data) – that would later become used in the decision-making process, i.e. in actual decision-making.

The design was exploratory since the aim was to provide knowledge on how and why policy makers made sense together and emerged at an agreement in producing the policy document. The study design consisted of observations and interviews. An exploratory study is used in areas where little is known or if the key objective is to understand how participants´ conceptions or values emerge through their speech and their narrative [47]. Since the aim of the study was to explore how the PSG reached collective agreement and how economic evaluations matter and are used in actual decision-making, I wanted to both observe the PSG work process and to carry out interviews in order to understand their views as well as the context of behaviour [51]. Observation involves the systematic and detailed observation and recording of what people say and do. Observations are useful in giving a descriptive picture of a process, i.e. course of events during a time period, and interviews are valuable to gain insight in to the perceptions and values of the informants by using their own language as a way of understanding and giving meaning [47].

A research interview is a professional conversation and an inter-change of views between two people [50]. It is a communicative event with a purpose - a structured conversation with an attempt ´to understand the world from the subject´s point of view´[50]. An in-depth interview is thus a method used to explore issues and involves a broad agenda, which maps the issues to be explored across the sample. In a interview, the emphasis on depth, nuance and the interviewees own language is a way of understanding meaning [47]. A key feature in in-depth interviewing is that it is intended to combine structure with flexibility. It is, for example harder to impose a structure in a group discussion or focus group. Key questions are often asked and the researcher also does some probing for further information. A second feature is that the interview is interactive in nature. Third, the researcher uses a range of probes and other techniques to achieve depth of answers in terms of penetration, exploration and explanation. It allows the researcher to put follow-up questions, and the informants the possibility to expand on the issues they found important. The interviewer uses follow-up questions to obtain deeper and fuller understanding of the participants meaning. In this study, I have chosen to use an interview guide that contained open-ended questions covering specific topics to explore the primary interest in the research questions, and also follow-up questions to explore the decision-making process and the role of health-economic evidence. Fourthly, the interview is generative in the sense that new knowledge or thought is likely, to be created, while the extent may vary. Interviewing is

preferable as the language used by participants is essential to gain insight into their perceptions and values [47, 52].

Both observation and interviewing methods supplement each other in explaining how participants in the PSG made sense, reasoned and what arguments were used in order to come to agreement. Documents associated with the PSG meetings, including information on the formal task of the PSG, the clinical and health-economic evidence used as decision support as well as information on the NBHW organization, were also read as background material, though not analysed in depth.

Data collection

Observations and field notes were taken in the period 2006 to 2008, by the author (NE) during all PSG meetings, with descriptions of the course of events. These observations contributed to a comprehensive picture of the PSG work process. Eleven full-day PSG meetings were held over the course of the work process, of which three meetings were of two days. Field notes were taken during all the meetings. The field notes included a description of the course of events; the data material was not selected nor categorized during the observations. The field notes taken from the observations were transcribed the same day or the day after the meeting, followed by data analysis.

The face-to-face interviews were conducted by the author (NE) in 2009. The PSG consisted of twenty-one members and interviews were conducted with nine members. All informants were approached after the PSG had completed their work, so as not to disturb or influence the course of events during the work process of producing the national guidelines. The sample for the interviews was strategically selected, with the help of a senior researcher, in an attempt to achieve diversity, to achieve broad representative coverage, including geographic distribution, and to assure that various clinical specialities were being represented. The health economist was not included in the sample, as the primary research question of interest was how the decision-making group (non-economists), in this case the PSG, used available economic evidence that was not in their field of expertise. Data collection was continued until "data saturation" or point of no new insights was perceived to be obtained from expanding the sample further [47]. The informants were contacted by e-mail with general information about the aims of the study, contact details and

information on informed consent. After a fortnight a reminder e-mail was sent. All informants approached agreed to participate (with the exception of one person).

An interview guide was designed with key questions against the background of the data generated from the observations. The guide contained open-ended questions, covering specific topics to explore the primary interest in the research questions, grouped into two sections; the role of health-economic evidence and the decision-making process (see Appendix 1). The specific topics addressed during the interviews were questions regarding: the use of cost-effectiveness data, what information and evidence was available and how these were made sense of and assessed during the group´s deliberations. Further topics regarding what worked/did not work in coming to collective agreement and what happened if another member in the PSG had an opposing opinion, were also of interest. The interview guide was tested on one informant to establish whether the interview guide would work or not and a few minor modifications made.

Also, potential follow-up questions, in parallel to Kvale and Brinkmann , were specified, which made the interview more dynamic [50]. The topic guide thus contained follow-up questions regarding issues concerning what happened if the PSG members had divergent and conflictual views, the way in which the group handled the practical tensions of coming to agreement, and the ambiguity of working within an EBP framework. Each interview took between one and two hours. After the interview more information was given on how the interview would be analysed and how the information would be reported. The informants were also assured that their statements would be treated confidentially in all presentations.

Data analyses

All interviews were transcribed verbatim for further analysis. Thematic content analyses were carried out, according to the common practice of interpretation of content, using an inductive approach [53]. Qualitative research is often viewed as predominately inductive, but both deduction and induction may be involved at different stages of the qualitative research process. Analytic induction involves an iterative process of defining a problem, then formulating and testing a hypothesis, and redefining the problem until all cases fit. Induction looks for patterns and associations derived from observations of the world. In

practice, abduction is often used in case-study based research processes. Abduction is used as a reflexive methodology and has its point of departure in an empirical basis, like induction, though does not reject theoretical preconceptions [54]. The empirical data is adjusted and refined.

The interviews were read in their entirety several times to get a sense of the whole. Thereafter, sentences were extracted which seemed important for the research questions. The purpose of the analysis was to condense the content while preserving the core and still mirror the content of the interviews. Thus, the primary research questions formed an initial structure for the categorizing of research data. Throughout the process of data collection, analysis patterns and recurrent topics, themes and sub-themes were identified. Early frameworks and concepts were treated as tentative and were repeatedly refined as new and existing data, was analysed. Finally, similarities and differences between the data, in both the observations and the interviews, were compared with other sections and checked to confirm whether different perspectives had been ignored.

Both Papers I and II were based on the same data set, i.e. the data collection was based on the same observation and interview material. However, the two papers addressed different research questions, which were mirrored in the interview guide. The data analyses thus covered different areas of research and were made separately.

The aim of Paper I was to explore the practice of EBP and to provide knowledge on how and why decision makers made sense together and emerged to at a collective agreement in producing the policy document that constitutes the national guidelines. The interest was to find out how the decision makers (the PSG) handled various forms of evidence and values. The specific topics addressed during the interviews were how the PSG made sense of evidence and assessed this during the group´s deliberations. The topics included the informant's understandings of the formal task, how they worked during the course of the process, how they came to collective agreement working with the policy document, what worked and what did not work in coming to agreement, i.e. what happened if another member in the PSG had an opposing opinion. During the interviews different issues were bought up, reflecting on the process of producing policy text, what the members in the PSG did during the course of the work, group composition, and the "rules" that applied in the group meetings were addressed.

As the main focus of Paper I was on the process arriving at a collective agreement, two main categories evolved during the course of data analysis to describe the activities used by the group. These were; group facilitating activities (as the research topic was on reaching collective agreement) and the ways in which the PSG chose to handle the task (what they actually "did"). Reaching agreement involves both the act of forming a (collective) group and the act of reaching agreement by resolving or avoiding deadlock in the deliberations to resolve practical tensions, i.e. moving the work process forward.

The aim of Paper II was to explore how economic evaluations matter and are used in actual decision-making. Specific topics were addressed during the interviews regarding the use of cost-effectiveness data as decision support in the PSG work process. Three main categories evolved during the course of the data analysis to address the primary interest of research. The focus was on how the PSG handled the evidence, what evidence was available and whether it was actually used and accepted by the members of the group. The explicit use of cost-effectiveness data and specific situations in which the data mattered also evolved during the data analysis. As this is a qualitative study, the interest was not in quantifying the level of use of cost-effectiveness data. Instead, the aim was to explore the inclusion of cost-effectiveness data as a basis for priority gradings. The main categories identified during the data analyses were; accessibility, i.e. available (cost-effectiveness) evidence used as decision support, level of understanding, acceptability, i.e. relying on and balancing available evidence, and the explicit use of cost-effectiveness data, i.e. used as a fine-tuning instrument to adjust to, and as a counterweight for, "dichotomisation".

Paper III

Systematic literature search strategy

An extensive systematic literature search on the available cost-effectiveness analyses of intervention strategies within the cardiovascular field, was conducted by the author (NE). The overall aim of the literature search was to compile scientific evidence on cost-effectiveness for the Swedish national guidelines for heart diseases in 2008. Further, the aim was to explore how cost-

effectiveness data may be presented, conveyed and communicated to decision makers, as well as looking at the advantages and disadvantages of so called cost-effectiveness ranking or league tables used as decision support.

Databases

The following databases were used to identify cost-effectiveness analyses for the literature search.

- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- Health Technology Assessment (HTA) Database
- MEDLINE/PubMed
- NHS Economic Evaluation Database (NHS EED)

Search terms and limits

The search term ´Heart Diseases´ was classified according to six disease group areas.

- Coronary artery disease
- Heart failure
- Arrhythmias
- Heart valve disease
- Inflammatory heart disease and congenital heart disease
- Secondary prevention and rehabilitation

Within each disease group, search terms were chosen in collaboration with a librarian. These search terms consist of diagnosis and standard medical treatment procedures reflecting the content of each group (Table 4).

Medical Subject Headings (MeSH) were used as search terms in MEDLINE/PubMed when available, and the search terms were extended with a free text search term when necessary.

NHS EED and HTA databases are economic databases. Thus, it was not necessary to include economic terms in the search strategy. In the medical databases, including MEDLINE/PubMed and CINAHL, the following economic search terms were used.

- Cost analysis
- Cost effectiveness
- Cost utility
- Life years saved
- Life years gained

- Quality adjusted life years
- QALY

In MEDLINE/PubMed, the search terms were used in the form of MeSH when available. MeSH terms may also be used in NHS EED and HTA. However, the database CINAHL uses its own so-called Subject Headings. In cases when the search strategy gave few or no search results using MeSH terms, the literature search was extended with a free text search term when necessary. The search was limited to publications in English from 2002 to 2006.

The search strategy was conducted according to the following principle: Heart Diseases [MeSH] + "Economic terms" (free text search of relevant economic search terms) + disease group [MeSH]. Table 4 presents an example of a search strategy using the MEDLINE/ PubMed database for echocardiography. The results of the literature search are provided in Table 5.

Table 4. Example of search strategy in MEDLINE/PubMed for Echocardiography.

Database
MEDLINE/PubMed

Limits
2002-01-01 – 2006-12-30 /English

Search terms

Heart Diseases [MeSH]	#1
"cost analysis" OR "cost effectiveness" OR "cost utility" OR "life years saved" OR "life years gained" OR "quality adjusted life years" OR QALY	#2
Echocardiography [MeSH]	#1 AND #2

Search terms: Adrenergic beta-Antagonists; Aggregation; Aneurysm, Dissecting; Angioplasty, Transluminal, Percutaneous Coronary; Angiotensin-Converting Enzyme Inhibitor; Aortic Aneurysm, Thoracic; Antagonists and inhibitors; Antilipemic agents; Aortic arch replacement; Aortic valve; Aspirin; Blood platelets; Cardiac rehabilitation; Cardiac stimulation; Catheter ablation; Cholesterol; Coronary Angiography; Coronary Artery Bypass; Creatinin; CRP; CT; Defibrillation; Digoxin; Diuretics; Echocardiography; Electrocardiogram; Electrocardiography; Endocarditis; Exercise Test; Glycoprotein inhibitor; Glycoproteins; Heart Catheterisation; Heart murmurs; Heart valve; Heart Valve Disease; Heart valve surgery; Hemoglobins; Heparin, Low-Molecular-Weight; Imaging; Implantable cardioverter defibrillator; Ischaemia monitoring; Lipids; Mitral valve; MR; Myocardial diseases /Cardiomyopathies; Myocarditis; Nitroglycerin; Pacemaker; Peak Expiratory Flow Rate; Pericarditis; Perimyocarditis; Permanent pacing; Platelet Aggregation Inhibitors; Potassium; Pulmonary valve; Radiofrequency ablation; Secondary prevention; Sodium; Statins; T4; Thrombolytic Therapy, TSH; Ultrasonography; X-rays. [1]

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[1] An additional search was conducted for the search term "imaging", including the search terms "CT" and "MR". The additional search terms were used together with the term Heart Disease and the economic search terms for all databases. This additional search resulted in 289 hits between the years 1990 and 2006. After careful consideration, only imaging methods used post 2000 were considered relevant. The extended search resulted in 51 relevant articles, and three articles were considered relevant for the cost-effectiveness ranking or league table.

Table 5. The results of the economic systematic literature search 2002-2006 (number of articles found).

Search Results	Arrhythmias	Coronary Artery Disease	Heart Failure	Heart Valve Disease	Inflammatory and Congenital Heart Disease	Secondary Prevention
Search Results	MEDLINE 62 CINAHL 13 NHS EED/ HTA 54	MEDLINE 263 CINAHL 65 NHS EED/ HTA 181	MEDLINE 121 CINAHL 15 NHS EED/ HTA 113	MEDLINE 13 CINAHL 2 NHS EED/ HTA 19	MEDLINE 7 CINAHL 5 NHS EED/ HTA 5	MEDLINE 101 CINAHL 36 NHS EED/ HTA 118
Total	129	509	249	34	17	255
Total (after removal of duplicates)	**104**	**425**	**216**	**29**	**16**	**215**
Total (after judged abstracts)	**29**	**77**	**34**	**7**	**4**	**33**
Total (after judged articles)	**19**	**34**	**9**	**0**	**2**	**16**

CINAHL, Cumulative Index to Nursing & Allied Health Literature; HTA, Health Technology Assessment Database; MEDLINE/PubMed; NHS EED, NHS Economic Evaluation Database.

Inclusion and exclusion criteria

A template was designed by the research group in order to judge the quality of the cost-effectiveness analyses for data extraction. This template was based on the criteria generally accepted by the health-economic community, and included a description of a well-defined intervention strategy and a clearly defined comparator for a specific patient population. Information on study design, costs and effects (outcome) and discount rates were noted. Studies reporting the outcome measures as a cost per QALY or LY gained were included.

After the initial database search, all the abstracts were read and judged by two examiners. Obvious irrelevant references were disregarded. Thereafter, the full references were acquired. Each article was once again judged by two examiners working independently. Articles that met the inclusion criteria but could not be adapted to a Swedish setting or included in the national guidelines, were excluded. Articles were also excluded when they did not constitute an economic evaluation or did not have the right outcome measure (QALYs or LY gained). In a few cases, the treatment strategy was considered dominant though the outcome measures, QALY or LY, were not used. The health outcomes were considered the same or better than the alternative treatment strategy at a lower cost and were reported as dominant (<0) per event avoided. An intervention strategy is considered dominant, i.e. is said to dominate another, when it has higher effectiveness and lower costs.

In the absence of cost-effectiveness data, decision-analytic modelling was used for a few special projects as part of the league table: foremost new intervention strategies. These special projects were integrated into the league table. Costs and effectiveness (health outcomes) of health interventions were estimated utilizing several sources to populate the model, using available data and adapted to a Swedish setting for the following intervention strategies:

- Implantable cardioverter defibrillators (ICD) for primary and secondary prevention
- Resynchronisation treatment (CRT) for the treatment of heart failure
- Drug eluding stents for patients with CAD undergoing percutaneous coronary intervention (PCI)
- Catheter ablation (RFA) for the treatment of AF
- Screening of young athletes for sudden death prevention

Compilation and exploration of the results from the literature search

The information compiled from the literature search was presented as a cost-effectiveness ranking or league table. To ensure that the cost-effectiveness data used for the different ranking or league tables complied with the 2008 version of the national guidelines, a medical expert was consulted. More than half of the results of the literature findings did not comply with the national guidelines. Only intervention strategies (and their comparators) as used in the Swedish healthcare system were included in the ranking or league tables, i.e. interventions not used in the Swedish healthcare system were excluded. The ICERs for these were converted into SEK and adjusted to the 2009 price level using purchasing power parities (PPPs) [55]. ICERs prior to 2002, from the previous edition of the guidelines, and were integrated. The same methods were used for both literature searches. The results were presented in terms of cost per LY or cost per QALY gained.

The results of the literature search were processed and categorized according to disease group area. An exploration was made of what factors matter when defining whether a cost effective intervention strategy aimed at, for example a low or high-risk patient group, greatly affects the ICERs. The results were also summarized and broken down, in order to convey as much information as possible in a simplified manner, for example defining whether an intervention strategy or medical technology is aimed at a low or high-risk patient group. Differentiations between different patient groups were made, for example in a single treatment strategy such as ICD.

Paper IV

Decision-analytic modelling approach

A decision-analytic modelling approach was used to estimate costs, health outcomes and incremental cost-effectiveness of a novel medical technology, radiofrequency catheter ablation (RFA), compared to the AAD for patients with symptomatic AF not previously responding to AAD. A lifetime time horizon was used. A modelling approach is appropriate when extrapolating end-points

over a long time horizon, i.e. in the absence of long-term data, and beyond the scope of a clinical trial. It is also useful when incorporating several sources of information as input variables.

The outcome measure, QALY, was used for the analysis according to common practice. The intervention strategy being analysed, RFA treatment, was a novel medical technology at the time of the analysis. Thus, a decision analytical approach seemed appropriate as well as making the model parameters probabilistic, i.e. defining probability distributions to reflect the uncertainty in evidence available for the input variables. As the intended use of the results was the Swedish national guidelines for heart diseases, both costs and health effects were estimated using Swedish data. Both costs and health outcome (QALYs) were discounted at 3 % per annum respectively, according to common practice in Sweden [56]. All costs are in 2006 prices and have been converted to USD using PPPs [55].

Model structure and underlying assumptions

A two-part model structure was used: a decision tree for the initial year in which the RFA procedure is assumed to take place, and a long-term Markov structure for subsequent years [57-59] (see Figures 2 and 3).

The short-term model provides the proportion of patients entering the long-term model health states after accounting for non-stroke mortality and stroke risk. Short-term clinical end-points, i.e. freedom of AF at 12 months, were used in the model. If the patient suffers a clinically significant relapse into AF, a second RFA procedure is usually offered as standard in Sweden and was assumed to take place during the initial year.
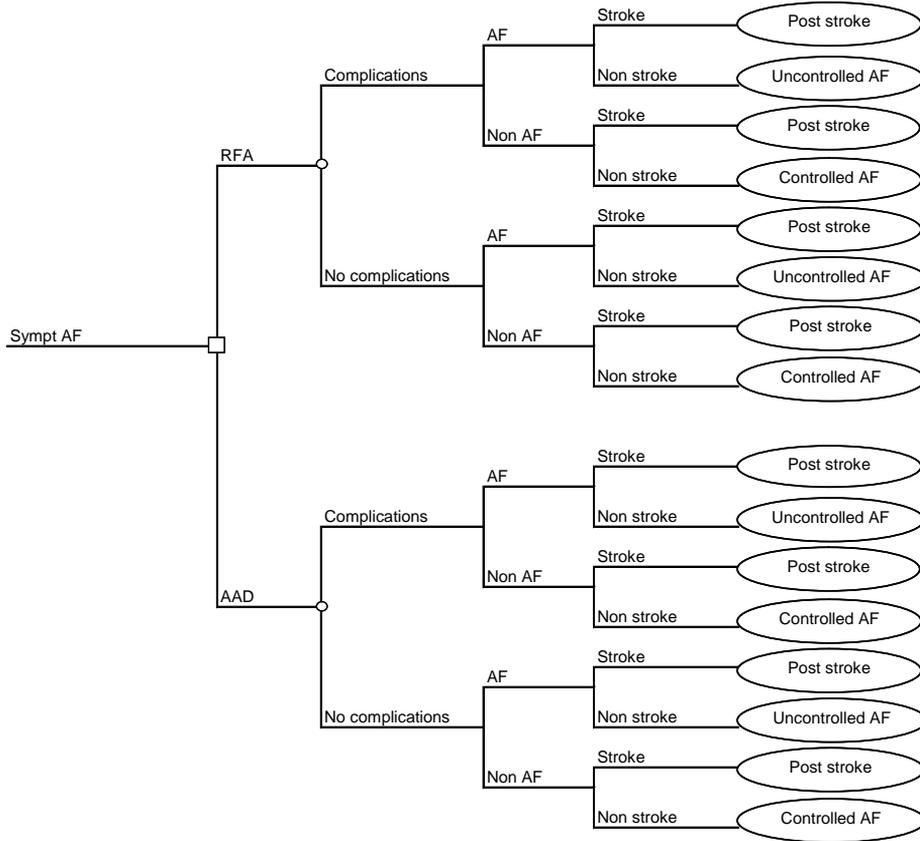
Figure 2. Short-term model structure.

The long-term, Markov, model structure was developed to extrapolate the lifetime costs and QALYs of the two intervention strategies. In a Markov structure, a hypothetical cohort of patients reside in mutually exclusive health states during intervals of equal length referred to as Markov cycles. The model consists of health states for controlled AF, uncontrolled AF, stroke and death. Separate health states for death, whether caused by stroke or another cause of mortality, were used. Annual Markov cycles were also applied.
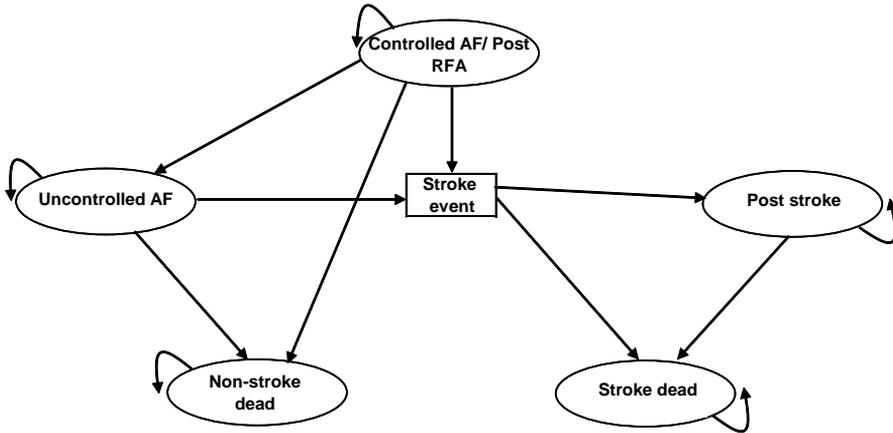
Figure 3. Long-term Markov model structure.

Successful treatment implies that the hypothetical patients enter the controlled AF health state. If the treatment strategy is not successful, the cohort of patients enters the uncontrolled AF health state. In the case of a stroke event, the cohort may enter the stroke dead or post-stroke health states. The ´post-stroke´ health state implies an elevated mortality risk and reduced QoL. Patients face a risk of non-stroke mortality and may make the transition to the non-stroke dead health state at any stage.

Model inputs

A summary of base-case model parameters is given in Table 6.

Table 6: Summary of model parameters.

VARIABLE	VALUE	REFERENCE
Probabilities		
Probability of AF free at 12 months RFA	0.780	[60-63]
AADs	0.090	[60]
Risk ratio RFA vs AAD	0.1017	Calculated
Stroke risk, AF (%)	1.5	[64]
Stroke risk, free from AF (%)	1.5	[64]
Complication with RFA	0.030	[65]
Cost items	*Mean costs; SEK (USD)*	
RFA procedure, single event*	90 000 (9 860)	[66, 67]
Complication cost	20 000 (2 190)	Assumption
AAD treatment, annual	15 000 (1 640)	[68]
Anticoagulation treatment, annual§	7 000 (770)	[69]
Cost of stroke (yr 1)	175 000 (19 180)	[70]
Cost of stroke (>yr 1, per annum)	40 000 (4 380)	[70]
QALY-weights for males in normal population	*QALY-weights*	
Age		
>69	0.830	[71]
70-79	0.800	[71]
80<	0.740	[71]
Decrement for AF	0.100	Assumption
Decrement for stroke	0.250	Assumption
Annual discount rate		
Costs	0.03	[56]
Effects	0.03	[56]

* Average cost for RFA procedure includes; 3-4 hospitalization days, diagnostic examinations for example ultrasound and/or CT and MR and catheters.
§ Anticoagulation treatment (warfarin) consists of; monitoring at specialist dept. (58 %), average cost per unit, 200SEK (22USD); number of visits per annum, 16.25; monitoring at primary care unit average cost per unit 545SEK (60USD) (42 % average cost 509SEK (56USD) of which 10 % at home, average cost 861SEK (94USD), number of visits, 13.75; travel, 42SEK (5USD); loss of production, 26SEK (3USD) and medication 576SEK (63USD).

Clinical effectiveness

A literature search was conducted to find data to populate the model. Clinical studies have shown a success rate for RFA, measured as freedom from AF relapses at 12 months, between 70 to 80 %, assuming that the intervention is repeated within a year in case of clinically significant relapse into AF or atrial tachycardia [72, 73]. Five randomized controlled clinical trials, reporting efficacy of RFA compared with AAD, were identified [60-63, 74]. One study was excluded as it only considered RFA as a first-line treatment, i.e. the patients did not receive AAD treatment prior to RFA [74]. The probability used for the decision-tree was based on the assumption that the intervention is repeated within the first year in case of relapse into AF, the standard procedure in Sweden. An average of 1.4 procedures per patient is needed to successfully isolate the pulmonary veins [65]. The yearly rate of AF and relative risk ratios for both a first and a second RFA procedure was calculated using randomized controlled clinical trial data [60] . After a follow-up periods of 12 months, 91 % (63/69) of patients still using AAD had at least one AF recurrence with the AAD treatment strategy [60].

Mortality and stroke risks

All AF patients, with at least one risk factor for stroke (CHADS2), benefit from anticoagulation treatment to reduce thromboembolic events. No evidence was found to indicate different stroke risks in the controlled AF and uncontrolled AF health states. The baseline risk of stroke was assumed to be 1.5 % for AF and non-AF on anticoagulation treatment using a conservative assumption [75]. The age-dependant standard mortality rates were based on the Swedish national data [76].

Costs

The short-term decision tree considered the costs associated with the RFA procedure. It was assumed that the RFA procedure was repeated within a year if not successful, implying an additional cost for the repeated procedure in the short-term decision tree. An RFA procedure was costed at 90 000 SEK [66, 67]. This cost includes 3 to 4 hospitalization days and diagnostic examinations for example ultrasound, CT /or MR and disposables such as catheters.

All complications used in the model were treated as costs. Complications associated with the RFA procedure include; tamponade, bleeding, pulmonary vein stenosis, stroke and oesophageal fistulas [77]. Deaths have been reported in some cases in connection with pulmonary vein stenosis and oesophageal

fistulas. In the Swedish national catheter ablation register, information on complications associated with RFA treatment was available. The probability of a major complication was assumed to be 3 % and no deaths were reported, based on Swedish clinical data [65]. There was no reliable data on the costs associated with different types of complications, thus an assumption was made.

Medical management for AF often involves the use of a combination of different medications. Both the RFA and AAD treatment strategy involves the use of AAD. The annual cost of AAD treatment has been estimated to 15 000 SEK. This cost includes hospitalisation, AAD medication and consultation, hospitalisation being the major cost driver for AAD [68]. In the long-term model, continued use of AAD after the initial year, was assumed in the case where RFA did not eliminate AF, i.e. not free from AF.

The average cost of monitoring AF patients using warfarin (anticoagulation) was 375 SEK per visit and 15 times a year, totalling 6 052 SEK per annum [69]. This cost includes the cost for monitoring, at either a specialist department or primary care unit, and actual medication. The cost of medication was estimated to 575 SEK per annum. The post stroke health state is associated with increased cost and the annual cost of stroke was assumed to be greater during the first year, based on the incidence of first-time stroke [70].

Health outcomes (QALYs)

No studies were found measuring QoL improvement on AF patients in a way that could readily be used for QALY weights. However, several studies have shown improved QoL after RFA treatment [17, 73]. For instance, QoL measured by the SF-36 instrument, improved significantly in all eight health dimensions after RFA treatment [78]. In order to estimate QALY weights for different health states, age-adjusted QALY weights based on a Swedish general population were applied for patients in the controlled AF state, and used as reference points. The QALY weights used in the model were 0.83, 0.81 and 0.74 for individuals aged >69, 70-79 and >80 [71]. Decrements were applied to the general population utility weight for the uncontrolled AF state and the post stroke state. An assumption made was using a decrement of 0.1 for uncontrolled AF and 0.25 for stroke to the baseline utility in the controlled AF state.

Ethical considerations

Ethical issues were considered and reflected upon throughout the course of this thesis. Established research ethics practice and ethical guidelines concerning: informed consent, assurances of confidentiality and the consequences of how the collected information would be used, were followed [47, 50, 79].

As previously stated, before the interviews were conducted, the informants were contacted by e-mail with general written information about the purpose and procedures of the research project. The information included contact details, information on informed consent, the voluntary nature of participation and the aims of the study. The information was written in conjunction with a senior researcher. Informed consent was obtained from all the participants before conducting the interviews. However, a reflection while conducting qualitative exploratory studies was that informed consent might pose difficulties as the nature of the study is exploratory and the researcher may have little advance knowledge of how the interviews and observations would proceed [50].

One consideration, before conducting the interviews, was also when to conduct the interviews in order not to disturb the course of events in the work process. The research group decided that the interviews should be conducted after the PSG had finished the process of work within the group and the interview guide was designed against the background of the data generated from the observations.

A researcher always needs to consider weighing up the scientific value of the added value of knowledge, against the possible risks in the form of negative impact on the research subjects [79]. Throughout the course of the work with the thesis, considerations have been given to how the statements and quotes are displayed to minimise the risk of identification. The informants were assured that their statements would be treated confidentially in all presentations. The informants not only have the right to withdraw from the study at any time, but also have the rights to anonymization, implying that possible identification through their comments should be eliminated.

The collected data material for this thesis came not only from the interviews, but was also data material collected through observations. The observations were thus part of the data collection for the thesis. As I was interested in

studying the process and practice of the national guidelines, I had access to the PSG meetings during the course of their deliberations and was thus privy to sensitive data material. I did not study the decisions made by the PSG after the decision-making process but was interested in studying the actual process. This puts me in a delicate situation when presenting the material from the observations, as well as from the open-hearted interviews that followed, where the informants played a more active part and provided me with valuable information. During the interviews a few informants disclosed information that they asked me not to share. I assured them that the purpose of the case study was to reflect the decisions and deliberations made by the PSG and that I had a responsibility to reflect the group as a whole. The results were to be as accurate and representative as possible, whilst made an effort to be as transparent as possible on the procedure from which I drew my conclusions.

Each interview began with a verbal description of the study and a recapitulation of the information sent by e-mail. Directly after the interview had been carried out, a more detailed description was also given of the study aims and also a description by the researcher/key investigator of the study plan and the fact that the collected information would be used for research purpose only. After the interview the author (NE) also explained how the interview would be analysed and how the information would be reported.

Another consideration was whether the Swedish law of ethical review was applicable to the research. In Sweden the ethical review, which is conducted by regional committees, in this case the Regional Ethical Review Board in Linköping, is ruled by: The Act concerning the Ethical Review of Research Involving Humans (2003:460) [80]. This law regulates research subject to the statute.

The research group came to the decision that ethical review was not required, according to sections 3-5, due to the fact that no sensitive personal data or personal data concerning offences against the law was collected or used. The Act concerning the Ethical Review of Research Involving Humans (2003:460) is applicable to research when the research 1. involves physical intervention affecting a person who is participating in the research, 2. is conducted in accordance with a method intended to physically or mentally influence a person who is participating in the research, 3. concerns studies of biological material that has been taken from a living person and that can be traced back to that person, 4. involves a physical intervention upon a deceased person, or 5. concerns

studies of biological material that has been taken for medical purposes from a deceased person and can be traced back to that person. The above does not apply to this research. In addition, the research does not involve a physical intervention affecting a person and the research was entirely based in Sweden.

RESULTS

This chapter presents the main results of the four papers included in this thesis.

Paper I

Several themes were identified showing how the PSG members handled various forms of evidence, made sense together and came to collective agreement on recommendations (priority gradings) that constitute the national guidelines for heart diseases. The two main themes identified were: (a) group facilitation activities and (b) avoiding deadlock in discussion, and their four identified under-categories (Table 7). These themes show the practical tensions, due to uncertainty and sometimes conflictual evidence, of coming to an agreement when producing recommendations. These will be further explained in this section.

Table 7: Identified themes for arriving at a collective agreement.

GROUP FACILITATING ACTIVITIES	AVOIDING DEADLOCK IN DISCUSSION
Making sense of the task through practical exercises	Creating new prioritization objects (POs)
Presence of a facilitator	Modifying existing POs resulting in a new "round" of discussions
Structured work and routinized work process	Use of cost-effectiveness arguments in cases of uncertainty and ambiguity
Using open deliberations as agreement seeking	Allowing particularly difficult POs more time and repeated deliberation

Group facilitating activities

Making sense of the task through practical exercises

The evidence provided by the groups of experts is adapted to operationalize the contents of the three ethical principles, i.e. the severity of a condition, the patient benefit-risk, and the cost-effectiveness. These principles were perceived as fundamental in the work process. However, most of the informants were not familiar with the framework for priority setting prior to the PSG work process. The task of the PSG thus became twofold; including the main task of setting priority gradings (recommendations in the policy text) and also becoming acclimatized and making sense of the framework used to produce priority gradings. The members of the PSG were exposed to written information, provided with verbal explanations of the formal task as well as practical exercises at an initial "boot camp". It was clearly stated that all PSG members must stand by all the decisions, i.e. reach collective agreement, and that all members of the group were responsible for all three hundred POs.

Presence of a facilitator

Group facilitating activities were identified as key factors in bringing the PSG members together as a group and organizing subjective, "conservative" and "radical" judgments. Here, the facilitator played an important role.

> *I think it is incredibly important that you get the right person for this… it is extremely important that the person can lead and guide this extremely heterogeneous group and its many strong-willed people. [I 2]*

Several informants brought up the role of the chairperson, who was perceived as a group facilitator playing an important and active role in encouraging both a disciplined and structured work environment, as well as driving the process forward; using encouragement, probing for answers without supressing debate, always inclined to stimulate debate etc.

> *Obviously, it's important to have a chairman, and there's no question that…it has to do with both acceptance and authority… and the perception that this is a person who doesn´t support any extreme point of view in any direction… you don't want that either… at the same time the person has to be someone who will drive the process forward … [I 1]*

Accordingly, the chairperson was perceived as a key actor in whom the PSG both placed their faith and felt encouraged to debate. The emphasis on scientific

facts became important in facilitating the group process and further in reaching collective agreement. The chairperson also stressed the importance of abiding by the "rules" and the PSG was "told off" when deviating from the framework, presented at the initial "boot camp", as a strategy to drive the process forward.

Structured and routinized work process

The members in the PSG created a particular work routine during the work process in order to structure what the PSG should be doing and how they should be doing it . Before each meeting, two members of the group had the specific responsibility of reading up on the scientific evidence related to certain POs, i.e. had "homework assignments". In practice, this meant reviewing the evidence provided by the experts - analysing the severity of the health condition, the effect of the treatment as well as its cost-effectiveness – according to the three ethical principles. The two members then presented their "homework assignments", i.e. the initial and preliminary priority grading proposal with a short statement for reasoning, to the other members in the PSG. During the course of the work each PO was also projected on a big screen, followed by a preliminary proposal for grading the POs. A general and open discussion then followed among the PSG, negotiating and trying to make sense of the evidence provided by the expert groups. Questions were asked, misinterpretations were clarified, the initial proposal was negotiated, modifications were made and agreed upon. By using this created routine the PSG members had a strategy of collectively making sense, and coming to collective agreement in order to set priority gradings in the production of recommendations.

> *Commitment is not enough if there's no structure. [I 3]*

The work process was characterized by "a disciplined work environment", as one informant explained, i.e. by taking personal responsibility for reading up on the evidence before each meeting. A structured work process thus enabled a heterogeneous group and its many strong-willed people to come to agreement.

Using open deliberations as agreement seeking

An activity used by the PSG during the whole work process was the use of open deliberations, openly justifying and reasoning through the scientific evidence when reaching a decision in agreement. The process of coming to an agreement was enhanced by using open deliberations where members were negotiating and where information was made sense of collectively. The informants

emphasised both the aspect of being encouraged to participate and the feeling of inclusiveness where everyone could contribute to the discussion.

> *I think the project management were clear right from the start that everyone was to get a chance to be heard…you felt it was okay to speak up if you thought it was important. In some instances I abstained from voting…but I feel the atmosphere in the group was clearly such that it was okay to put your thoughts out there, it was okay to strongly disagree and question things, and the fact that we were supposed to reach a consensus, that everyone who had an opinion should speak now and not later, that you would have to go along with the grading – I don´t have a problem with that. [I 1]*

> *Nobody who just wanted to hear their own voice or felt they had to say something every time – everyone was free to speak. [I 3]*

The PSG members were encouraged throughout the process to use open deliberations and to negotiate by testing each other and using arguments to persuade. The above quotes also emphasise capacity to keep an open mind to others people's points of view.

> *I felt that you sort of fought for a long time for the position you thought was best, but then you reached a consensus and I think that was good. It wasn't like 'Oh, let's get to this consensus before lunch – quickly'… there was lots of debate... but you had the aim of reaching a consensus – everyone did. [I 2]*

However, it was not always the case that everyone agreed:

> *…so there was some kind of consensus in the whole group that, yes, we'll probably make a grading three or a four or whatever it was. And no doubt it may sometimes have had, been affected, yeah, in other words, some disagreement and then I would have, I would have wished that somebody had documented this and… perhaps written down the arguments for and against … And you would have thought, even if there had been the slightest disagreement about the priority setting grading, in the consensus or whatever you might call it… And then you might have set out the arguments in favour of it in writing. [I 7]*

The act of discussing in order to make sense collectively, as well as negotiating with the aim to persuade, was apparent in the working process.

Avoiding deadlock in discussions

Another identified theme in order to arrive at collective agreement was avoiding deadlock in open discussion in order to move the process forward.

Creating new prioritization objects (POs)

The PSG's work consisted not only of reaching a priority grading, but also a discussion about the need to re-draft and supplement the existing POs, or as the members in the PSG named it: the "creation of new POs". Creating new POs became one way to avoid any deadlock in the discussion in order to advance the work, and also one of the most common explanations of what the task in the PSG consisted of according to the group members themselves. As one informant conveyed:

> *Priority objects were paraphrased and we were also invited to suggest new priority objects. [I 8]*

Thus, another important way to overcome deadlock was in activities where the members were paraphrasing as well as going back to the underlying evidence for the POs, in order to make sense of how to understand the data in different situations.

Modifying existing POs resulting in a new "round" of discussions

The members of the PSG had difficulties in reaching agreement when the POs were associated with limited or lack of evidence. Commonly, it was easier for the group to reach agreement on high priority gradings, and consequently, POs with low gradings gave rise to longer discussions. POs were changed, added and sometimes aborted. Accordingly, the work process was dynamic and iterative and when the PSG members were modifying POs, this resulted in new rounds of discussions and making sense collectively. As a contrast to the predetermined strategy, every meeting in the work of the PSG became interactive and in many ways creative in the sense of finding forms of making sense collectively.

Use of cost-effectiveness arguments in cases of uncertainty and ambiguity

Incorporating cost-effectiveness data into the decisions is a distinguishing feature in the Swedish national guidelines, in accordance with the model used as a framework for priority setting. Though the recommendations (priority gradings) produced by the PSG were often primarily based on clinical evidence. One reason for this was that cost-effectiveness data was often lacking. However, an interesting observation was that cost-effectiveness data played an important

role in cases of greater uncertainty and ambiguity, and when the PSG had difficulty in reaching agreement on how to set the priority gradings when the overall evidence base was weak. Consequently, the use of cost-effectiveness arguments clearly became a part of the PSG deliberation in cases of uncertainty. The use of cost-effectiveness data could therefore be regarded as a format for moving the work process forward, avoiding blocks in discussion, and viewed as a "solution" to solve the task of making a recommendation. Using cost-effectiveness arguments was also used to structure the discussions and interestingly was not challenged to the same extent as clinical evidence.

Allowing particularly difficult POs more time and repeated deliberation

Certain POs were discussed at several meetings. In these cases the facilitator had an important role in allowing particularly difficult POs more time in discussion, and to be brought up on several occasions. This also became a way of avoiding deadlock. Commonly, no POs were left without being openly discussed by the PSG members. However as identified in the observations, as a last resort at the end of a long working day, though POs were never left unheard, "fatigue" was a way to reach agreement on priority gradings. The members of the PSG raised concerns and made modifications, which often resulted in new discussions - group discussions.

Paper II

Several themes were presented in Paper II investigating how the PSG used cost-effectiveness data in making priority gradings. The main themes identified were: (a) accessibility (available cost-effectiveness data and level of understanding), (b) acceptability (reliance and faith placed in the evidence) and (c) use of cost-effectiveness data to form priority gradings (Table 8) and will be further explained in this section.

Table 8. Identified themes for the use of cost-effectiveness data in priority gradings.

ACCESSIBILITY	Available cost-effectiveness data to inform decisions
	Level of understanding
ACCEPTABILITY	Reliance on available evidence
	Balancing available evidence
USE OF COST-EFFECTIVENESS DATA	Dichotomisation
	Adjusting priority gradings

Accessibility

The PSG either had access to compiled information or lacked cost-effectiveness data, i.e. the work sheet was empty. The worksheet included a box specifically for cost-effectiveness data and was thus an integral part of the evidence base. Cost-effectiveness data was available for 57 of the 331 POs. When cost-effectiveness data was available, the POs could each be based on several underlying studies. For 139 of the POs, a qualified estimation (low-moderate-high cost per QALY) was made by the health-economic experts after consultation with the medical experts. Often, cost-effectiveness studies were lacking, i.e. the boxes were empty for 135 of the POs.

Available cost-effectiveness data to inform decisions
The informants reported that cost-effectiveness data is crucial to inform decisions on priority gradings. A specific box for cost-effectiveness data in the worksheet also reinforced the belief that economic evidence is important for the decision-making process. One informant pointed out that the use of data in the decision-making process was something to be proud of - "we ´dared´". Others pointed out that it distinguished the guidelines from their European counterparts, as the following comment highlights:

> *It is a strength that other countries do not have. [...] In my experience, they are lagging [in Europe] [A 4]*

The observations showed that PSG members were exposed to a lot of information before each meeting. The sheer number of POs in the guideline

document was more than 300. The members were consistently reminded by the chairperson and members of the steering committee to include economic aspects when forming priority gradings.

Level of understanding

Several informants identified that they had limited access to in-depth written materials and also a limited understanding of health economics. One informant commented:

> I don´t believe very many people have read this [the health-economic facts document], and there is widespread ignorance about it. So, there are short-falls in our understanding [A 2]

The informants were concerned about the lack of cost-effectiveness data and found it difficult to always make use of cost-effectiveness arguments in the decision-making process. A few informants questioned the results of model-based approaches and mentioned their limited understanding of the underlying assumptions in cost-effectiveness studies. For example, one informant commented:

> Now and then there were studies, but many boxes were empty. The health-economic evidence base was a more or less weak foundation the whole time [A 3]

Acceptability

Reliance on available evidence

The informants identified that there is an acceptance of and interest in health economics, specifically within the cardiovascular field, as the following comments suggest:

> There is a self-confidence in heart care. We know that we give ´value for money´ [A 3]

> Cardiologists have a higher awareness of health economics than do others in the medical profession [A 1]

The informants also perceived the health economist, who was present during the entire process, to be a credible representative of the health-economic academic community. A recurrent theme that the informants brought up was

their reliance on a health economist during all meetings, as expressed by the following comment:

> *When you are ignorant and don´t understand something, you tend to disregard it and accept some easy interpretations. So I think the fact that they have put a health economist in place here means a lot [A 9]*

A concern relating to poor levels of understanding was that too much faith might be placed in the use of cost-effectiveness data. An informant expressed that health-economic evidence *"becomes a ´truth´"*, and another informant said that the cost-effectiveness evidence, when available, was never questioned. A further informant's comment connected to this theme, is as follows:

> *I believe that owing to general ignorance, when you don´t understand something, you sometimes trust the written word and such, and there is this tendency, of course, because several big names [senior authorities] think this [health economics] is an acceptable science [A 2]*

An interesting finding was that other informants conveyed that their faith increased when the health economist identified and expressed a lack of evidence. Many informants realised that an evidence-based approach does not always signal the presence of randomised controlled trials. It also involves accounting for the lack of evidence, indicating a limited evidence base, as the following quoted comment suggests:

> *I appreciated the fact that [the health economist] also said there was no evidence. Evidence-based medicine is not only about finding the best studies with the highest grade of evidence, but is also about expressing the lack of evidence. Indicating a lack of evidence and making an educated guess wins respect [A 3]*

Another theme expressed by the informants was the use of cost-effectiveness data perceived as a means of obtaining healthcare resources such as new expensive medical technologies. One particular informant indicated that cost-effectiveness data was not perceived as a threat but rather as a useful decision tool. An example of this theme is catheter ablation treatment, which is illustrated later in this paper.

Balancing available evidence
The informants generalised that the cost-effectiveness data was important in reaching a decision and that they did not primarily consider economic

arguments. Cost-effectiveness was not reviewed and challenged to the same extent as clinical evidence, as indicated in the following comment:

> *Now and then, it came up, but not at all in the same manner as for those who had written the medical facts [A 1]*

Thus, cost-effectiveness data was seen as a supplement to clinical evidence. Primarily, the informants considered both clinical effectiveness of the treatment and the associated risks when reaching a decision, and secondly, cost-effectiveness data.

Use of cost-effectiveness data

Dichotomisation

When asked to reflect on situations when economic arguments were used in the decision-making, i.e. making priority gradings, a majority of informants had difficulty in isolating the cost-effectiveness data from the collected evidence base. Many informants pointed out that they had doubts about using the evidence base when it was weak, although they had to take a position in order to make priority gradings.

The findings suggest that the PSG found it difficult to spread the priority gradings evenly on the 10-grade scale. The group tended to award either a high or a low grading, which resulted in a *U-shaped curve,* i.e. a majority of priority gradings entailed either high or low rankings and were adapted to become a Yes or No answer. Of the 300 POs, only 31 were ranked 5 or 6. Thus, dichotomising the POs in terms of favouring (high rankings, 1 to 4) the medical condition and intervention, or disfavouring (low rankings, 7 to 10) the treatments, was used as a solution in making priority gradings. The groups´ deliberations were characterised by the need for new POs and creating new POs was often used as a strategy to move the work forward, resulting in dichotomisation.

Adjusting priority gradings

Even if the informants had difficulty giving examples of the specific use of cost-effectiveness data, the observations show that economic arguments were used after a preliminary priority grading had been made that *favoured* or *disfavoured* the treatment. A ranking 1 to 3 signalled that the PO *will be* carried out in

medical praxis, a ranking of 4 to 6 signalled that it *ought to be* carried out, and a ranking of 7 to 10 signalled that it *might be* carried out. A ranking of 10 indicated that a PO was used as an exception in medical praxis and only in cases of affordability. Thus, economic arguments were used in the group's deliberations after dichotomisation to adjust the priority gradings.

The availability of cost-effectiveness data did not always conclude that high ICERs would imply low priority grading. Certain POs were given high rankings even though the cost per QALY was judged to be high. The PSG members interpreted that society is willing to pay more for severe diseases, i.e. when need was considered, thereby, influencing the priority gradings. The findings from the observations indicate that it was easier to make priority gradings for high rankings, even when cost-effectiveness data on such strategies as life-saving intervention was lacking.

Examples of situations of where cost-effectiveness data is used

The following examples have been chosen to highlight cases when the PSG made use of cost-effectiveness data in their decision-making.

Implantable cardioverter defibrillators

Cost-effectiveness data that was available for both secondary and primary preventive use of ICDs varied depending on the risk of sudden death, from a moderate (100,000 ≤ 500,000 SEK) to a high (500,000 ≤ 1,000,000 SEK) cost per QALY gained compared with the cost-effectiveness data for AAD. The higher the risk of sudden death, the lower the cost per QALY gained. The secondary preventive use of ICDs was given a ranking of 2, and the primary preventive use was given a ranking of 4.

Economic arguments were used during the group's deliberations focusing on the implication on budget impact of a high priority grading. Arguments were based on the survival benefit for the patient population as a whole, including QoL measures. The survival benefits were weighted against the increased cost of the device. Initially, the PSG made a decision in favour of the treatment and thereafter cost-effectiveness data was included in the discussion. The implications of the implementation of expensive medical technology, such as ICDs, were discussed. Although ICDs are potentially life-saving devices for

people at risk of sudden death as a result of cardiac arrhythmias, it was not given the highest ranking of 1.

Table 9. Examples of priority gradings for ICD.

Medical condition *Intervention*	Severity of the condition	Effect of intervention	Evidence of effect	Cost per LY/ QALY gained	Health-economic evidence	Ranking**
Risk of sudden death for patients with ischemic heart disease, impaired ejection fraction (EF ≤ 35 %) and function class NYHA II-III at least 3 months after MI, in spite of optimal medical management for heart failure *ICD* *(primary prophylaxis)*	High risk of premature death Low to high need of symptom relief Low to major impact on quality of life.	Moderate to high reduction of risk for premature death No to low effect on symptoms Positive to negative effect on quality of life Low to moderate risk for pre- and post-operative complications	Evidence level 1 for reduction of risk for premature death	**ICD vs. conventional medical management** **Moderate to high ***	**Good scientific evidence**	**4**
Ventricular arrhythmia (VT/VF) with cardiac arrest or syncope for patients with/ without impaired left ventricular function *ICD* *(secondary prophylaxis)*	High risk of premature death High need of symptom relief Major impact on quality of life	Moderate to high reduction of risk for premature death Low to high reduction on symptoms No to high improvement on quality of life Low to moderate risk for pre- and post-operative complications	Evidence level1 for reduction of risk for premature death compared to medical management	**ICD vs. conventional medical management** **Moderate to high ***	**Good scientific evidence**	**2**

ICD, Implantable cardioverter defibrillator; LY, Life-year; MI, Myocardial infarction; NYHA, New York Heart Association; QALY, Quality adjusted life year; VF, Ventricular fibrillation; VT, Ventricular tachycardia.
*Low (≤ 100,000 SEK (11,000 Euro)); Moderate (100,000 ≤ 500,000 SEK (11,000 ≤ 55,000 Euro)); High (500,000 ≤ 1,000,000 SEK (55,000 ≤ 111,000 Euro)); Very high (>1,000,000 SEK (111,000 Euro) cost per QALY gained.
**1 denotes an intervention with the highest priority ranking and 10 with the lowest.
Source: National guidelines for cardiac care 2008. Table annex to decision support document – Medical conditions and interventions for heart diseases [translated].

Catheter ablation treatment

The PSG faced difficulty in reaching a priority grading in the case of catheter ablation used for the treatment of patients suffering from symptomatic AF. Cost-effectiveness data, in the form of a simple model calculation, had been provided by the health-economic expert group for the group's deliberations. Thus, the steering committee identified the need for cost-effectiveness evidence as a basis for the PSG's decision-making. The deliberations were adjourned several times in the course of the work, and significant time was spent considering the signal value of the decision. The group was concerned about the long-term efficacy of the treatment and a lack of cost-effectiveness data.

Despite its higher initial intervention costs, catheter ablation treatment was considered a cost-effective intervention compared with medical management and was estimated at a low (≤ 100,000 SEK) cost per QALY gained for patients who previously failed to respond to medical management. The PO was finally given a priority grading of 4. The PSG's decision reflects the fact that new cost-effectiveness data has become available, justifying a decision in favour of the treatment. Thus, the treatment ought to be considered as an alternative for patients who have not responded to previous medical management.

Table 10. Example of a priority grading for catheter ablation.

Medical condition *Intervention*	Severity of the condition	Effect of intervention	Evidence of effect	Cost per LY/ QALY gained	Health-economic evidence	Ranking* *
Symptomatic or persistent AF in spite of adequate antiarrhythmic medical management *Catheter Ablation*	Low to moderate risk of premature death High need for symptom relief Major impact on quality of life	Favourable effect on symptomatic AF (56-86 %) 1-6 % serious complication risk, including low mortality risk Unknown effect on risk of premature death	Good scientific evidence	**Catheter ablation vs. antiarrhythmic drug treatment** **Low***	**Good scientific evidence**	4

LY, Life-year; QALY, Quality adjusted life year.
*Low (≤ 100,000 SEK (11,000 Euro)); Moderate (100,000 ≤ 500,000 SEK (11,000 ≤ 55,000 Euro)); High
(500,000 ≤ 1,000,000 SEK (55,000 ≤ 111,000 Euro)); Very high (>1,000,000 SEK (111,000 Euro) cost per QALY gained.
**1 denotes an intervention with the highest priority ranking and 10 with the lowest.
Source: National guidelines for cardiac care 2008. Table annex to decision support document – Medical conditions and interventions for heart diseases [translated].

Clopidogrel plus ASA (aspirin)

Clopidogrel is used with acetylsalicylic acid (ASA) for the treatment of unstable angina as a secondary prevention of PCI for 3 to 12 months. ICERs were estimated at a low (≤ 100,000 SEK) to moderate (100,000 ≤ 500,000 SEK) cost per QALY gained for the combination of clopidogrel and aspirin versus aspirin alone.

During the group´s deliberations, the members´ arguments primarily concerned the medical evidence, i.e. avoidance of ischemic events weighted against the excess risk of bleeding. The PO was finally given a high priority of 3, reflecting the low ICERs and the evidence that was available for the intervention. The high-ranking decision may be viewed against the previous edition of the guidelines when clopidogrel was given a low-ranking decision reflecting the sparse cost-effectiveness evidence then available.

Table 11. Example of priority grading for clopidogrel.

Medical condition *Intervention*	Severity of the condition	Effect of intervention	Evidence of effect	Cost per LY/ QALY gained	Health-economic evidence	Ranking**
Unstable coronary artery disease *Clopidogrel plus ASA, 3 to 12 months*	Moderate risk of premature death	ASA + clopidogrel, compared to ASA, reduced (non-fatal MI, stroke or cardiovascular death), from 11.4 to 9.3 (RR 0.80, CI 0.72-0.90) No significant difference in cardiovascular death separately. Increase in major bleeds from 2.7 to 3.7 % (RR 1.38, CI 1.13-1.67)	Good scientific evidence	**Clopidogrel vs. standard treatment (ASA)** **Low to moderate***	**Good scientific evidence**	**3**

ASA, Acetylsalicylic acid; CI, Confidence interval; LY, Life-year; QALY, Quality adjusted life year; RR, Relative risk.
*Low (≤ 100,000 SEK (11,000 Euro)); Moderate (100,000 ≤ 500,000 SEK (11,000 ≤ 55,000 Euro)); High
(500,000 ≤ 1,000,000 SEK (55,000 ≤ 111,000 Euro)); Very high (>1,000,000 SEK (111,000 Euro) cost per QALY gained.
**1 denotes an intervention with the highest priority ranking and 10 with the lowest.
Source: National guidelines for cardiac care 2008. Table annex to decision support document – Medical conditions and interventions for heart diseases [translated].

Paper III

More than a thousand abstracts were identified and read by the author and a co-researcher, and over a hundred complete bibliographical references were acquired and judged. Cost-effectiveness analyses that met the selection criteria was used and provided sufficient information for more than two hundred cost-effectiveness ratio estimates. One hundred and thirty nine of these could be referred to Swedish treatment strategies used in the guidelines, ranging from dominant to those costing more than 1,000,000 Euros per QALY or LY gained.

The main results are presented in the cost-effectiveness ranking or league table (Appendix 2). The table is separated into five sections. The first column contains the intervention strategy and the compared intervention and disease group, the second column contains patient population and possible sub or risk group, and the third column contains ICERs presented as cost per QALY or LY gained. The fourth column includes information on the society from which the data

originates, and the fifth column contains study references from which ICERs were drawn.

The cost-effectiveness ranking, or league table, was categorised according to disease group areas. The majority of ICERs refer to treatment strategies for acute CAD and stable angina, followed by arrhythmias, heart failure and congenital heart disease (Table 12). Thus, instead of presenting one long list of ICERs, each disease group constitutes its own cost-effectiveness ranking or league table and may be broken down further when categorised for specific interventions. Within each category, there were several cost-effectiveness studies that referred to the same intervention strategy. For example, in the case of stable angina, 23 ICERs were found corresponding to 10 POs, i.e. categories of interventions in the national guidelines for heart diseases.

Table 12. The Swedish national guidelines for heart diseases statistics.

Statistics	Number of POs
POs in the Swedish national guidelines for heart diseases in total	339
POs in the league table corresponding to a PO in the Swedish national guidelines for heart diseases	42 (139)
Acute coronary artery disease (CAD)	*14 (63)*
Stabile angina	*10 (23)*
Arrhythmias	*10 (32)*
Heart Failure	*7 (19)*
Congenital heart disease	*1 (2)*
POs where cost-effectiveness evidence was lacking	294

Despite the fact that the literature search resulted in more than one thousand articles, cost-effectiveness evidence is absent in 294 POs. One reason for this is that several new POs were ´created´ during the course of the work process. Most of the ´new´ POs refer to diagnosis. Thus, the cost-effectiveness literature search was not comprehensive. However, the most important POs were included in the literature search. As previously mentioned, in the absence of cost-effectiveness data, decision-analytic modelling for a few special projects was used as part of the league table. Several POs were also estimated in collaboration with medical expertise.

Table 13 represents ICERs for primary prevention with implantable cardioverter defibrillators (ICDs) compiled for the national guidelines. In this case, ICERs for a single treatment strategy, i.e. for the same medical technology, ICDs, are presented in the table. The table conveys cost-effectiveness data in a simplified manner by categorizing, summarizing and breaking down the results from the literature search. Primary preventive use of ICDs is aimed at high risk individuals with an increased risk of sudden cardiac death, i.e. for patients with a previous history of myocardial infarction (heart attack) and heart failure.

Table 13. Cost-effectiveness ratios for primary prevention with implantable cardioverter defibrillators in Euros (2009).

Intervention and compared intervention strategy	Patient group	ICER, Euro per QALY or LY gained	References
ICD vs. antiarrhythmic drug treatment (amiodarone) for patients with arrhythmias	High risk patients	33 890 /QALY	Owens et al. [81] (2002)
ICD vs. antiarrhythmic drug treatment (amiodarone) for patients with arrhythmias	Moderate risk patients	51 590 /QALY	Owens et al. [81] (2002)
ICD vs. antiarrhythmic drug treatment (amiodarone) for patients with arrhythmias	Low risk patients	109 350 /QALY	Owens et al. [81] (2002)

ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; LQTS, long QT syndrome; LY, life year; QALY, quality adjusted life year.

Defining whether an intervention strategy is aimed at a low or high-risk patient group greatly affects the ICERs. By presenting the ICERs for patients with high and low risk of sudden cardiac death respectively, the results may be communicated and made accessible to decision makers. A high-risk subgroup of patients resulted in an ICER of 33,890 Euro per QALY gained and a low-risk subgroup resulted in 109,350 Euro per QALY gained [81]. This piece of information is crucial to decision makers when prioritizing scarce healthcare resources, i.e. optimizing the number of patients and which patients might benefit from the treatment. The ICER for any specific medical technology may be categorised according to age, gender and other risk factors thus affecting the ICERs.

Therefore presenting and communicating the results constitutes a first step in making cost-effectiveness data accessible to decision makers. The whole ranking or league table represents one example of how this may be done. Table 13 thus provides an additional example of how a ranking or league table may be broken down and communicated to decision makers.

Paper IV

Results of base-case analysis

The base-case results of the cost-effectiveness analysis show that the RFA treatment strategy was associated with an incremental gain in QALYs and reduced costs compared to the AAD strategy. This implies that the RFA was considered a cost-effective treatment strategy in a lifetime perspective, despite higher initial intervention costs compared to AAD.

The model was run probabilistically, i.e. allowing uncertain parameters to vary randomly within predefined distributions reflecting the overall uncertainty of model parameters. The results of the base-case analysis are shown in a cost-effectiveness plane illustrating the thousand simulations (Figure 4). The vertical axis represents the difference in costs, and the horizontal axis represents the difference in health outcomes for the two treatment strategies. The plotted results imply that most of the ICERs are more effective and less costly in the south east quadrant, and more costly in the north east quadrant. If the benefits of the RFA treatment strategy are sustained during a lifetime, the RFA treatment strategy would be the optimal one, i.e. most of the ICERs are placed in the south east quadrant.

Cost-effectiveness plane
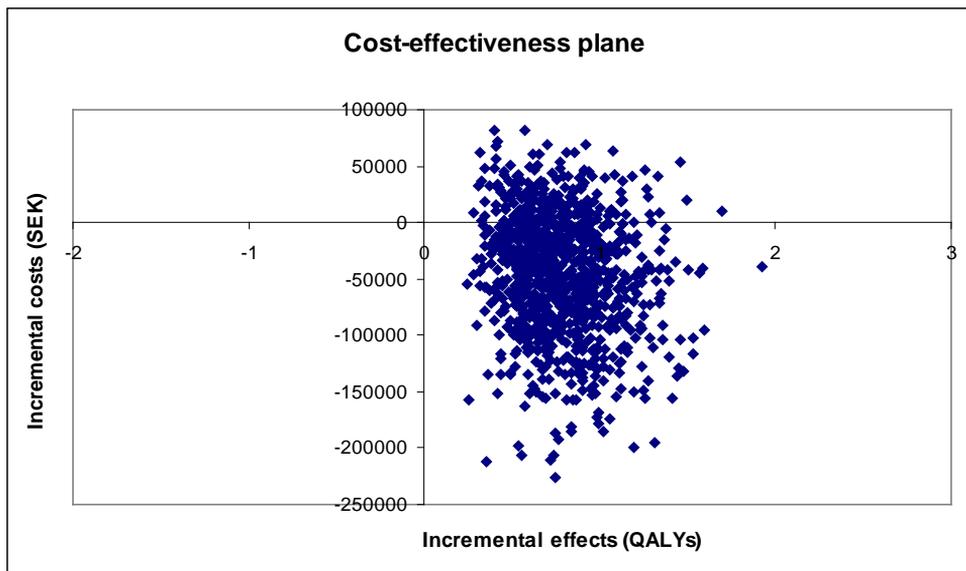
Scatterplot diagram to illustrate uncertainty in the results of the analysis. Each point represents the result from one simulation run based on parameter values drawn from pre-specified statistical distributions. Results measured in additional (incremental) costs and QALYs gained (incremental effects) by replacing AAD with RFA in the lifetime analysis. The SE quadrant implies a treatment strategy associated with reduced costs and incremental gain in QALYs, i.e. is considered a dominant treatment strategy.

Figure 4. Cost-effectiveness plane of probabilistic base-case analysis of RFA vs. AAD.

Alternative scenarios

To assess whether the results were affected by changes in the model assumptions, one-way deterministic sensitivity analysis was also performed Two key parameters were found to be most important; the reversion rates of the RFA procedure back to AF and variations in stroke risks in the different health stated in the model. The results of the analysis thus depend on whether the long-term positive effect of RFA is maintained over a lifetime period, i.e. patients remain free from AF. No long-term clinical studies were found with data beyond a 12-month follow-up period. Different annual reversion rates (5 %, 10 % and 15 %) back to uncontrolled AF after RFA were thus considered in the alternative scenarios (Table 14).

The results of the analyses were sensitive to the rate of reversion back into AF, implying both decreasing QALYs and higher costs for the RFA treatment strategy. Even though the results were sensitive to reversion back into AF, the

costs of RFA are only slightly higher compared to the AAD treatment strategy. The benefits (QALYs) of RFA are always higher than that of the AAD strategy in the alternative scenarios. In spite of the higher costs and decreasing QALYs for the RFA strategy, Table 14 should be interpreted by combining both costs and benefits in the ICER column. For all values tested, the ICERs were below the threshold value for what is considered to be cost-effective (ranging from dominant to 440,800 SEK (48,310 USD)).

Conservative estimates for the stroke risk were used in the base-case analysis. Whether the elevated stroke risk in the AF health state is eliminated with the RFA treatment strategy, is unclear. In the base-case analysis, an annual rate of 1.5 % was used as an estimate for both controlled and uncontrolled AF. In the sensitivity analysis, the stroke risk was varied in the uncontrolled AF health state. There are more patients in the AF state in the AAD treatment strategy. Therefore the AAD treatment strategy was more sensitive to variations in stroke risk. Thus, an elevated stroke risk for the AF state will decrease health outcomes in the AAD strategy disfavouring the AAD treatment strategy.

Table 14. Quality adjusted life years and incremental cost-effectiveness ratios for RFA compared with AAD treatment.

Intervention	QALY	Cost SEK (USD)	ICER SEK (USD)/ QALY)
Probabilistic base-case analysis			
RFA	9.46	232 300 (25 460)	**Dom**
AAD	8.68	277 700 (30 440)	
Annual probability of reversion to uncontrolled AF after RFA			
5 %			
RFA	9.06	318 600 (34 920)	75 500 (8 280)
AAD	8.55	279 700 (30 660)	
10 %			
RFA	8.91	366 400 (40 160)	241 400 (26 460)
AAD	8.55	279 700 (30 660)	
15 %			
RFA	8.81	395 300 (43 330)	440 800 (48 310
AAD	8.55	279 700 (30 660)	

ICER, Incremental cost-effectiveness ratio; QALY, quality adjusted life years; RFA, radiofrequency ablation treatment; AAD, antiarrhythmic drug treatment. Dom, dominant.

DISCUSSION

This chapter comprises a discussion of methodological considerations and the main results of the four papers included in the thesis.

Methodological considerations and discussion of the main results

This thesis has used different analytical approaches in the four papers. The thesis, as a whole, may be seen as a case of mixed methods to study the use and presentation of economic evaluations in health policy decision-making.

Papers I and II involve the use of both observations and in-depth interviews as research methodologies, which is a strong point in the study design. The discussion in all PSG meetings gave insight into the entire work process. The interviews supplemented the findings from the observations. Reliability is generally concerned with the replicability of the research findings, i.e. whether the findings may be repeated or not. It is often avoided in qualitative research, but in its broadest sense might be essentially explained as the collective nature of the phenomena under study, i.e. what might be expected to be consistent [47]. Another dimension is whether the findings (constructions placed on the data) have been consistently derived. In practice, the researcher should ask whether the study design and selection is without bias, whether the fieldwork is carried out consistently, whether interpretations are carried out systematically and whether the design allowed equal opportunity for all perspectives. The study design did not include all members of the PSG being interviewed. The informants were clinicians working in specialist units in the cardiovascular field and had a high awareness and widespread acceptance of the use of cost-effectiveness data in priority gradings. This includes the use of cost-effectiveness data as a means of obtaining new expensive medical technologies, specifically in the cardiovascular field. The cardiovascular field is favoured by a huge body of knowledge, and decisions are often based on well-constructed clinical trials and available cost-effectiveness studies [2]. Further research is needed to confer the results of this study on other disease areas. However, the process and practice of reaching agreement in decision-making processes may be applicable to other decision-making groups.

Within qualitative research, however, internal and external validity is more commonly used to verify the study findings. Validity concerns whether the researcher is reflecting the phenomena under study, as perceived by the study population, i.e. the correctness of the findings [47]. Both internal and external validity are strongly linked. To verify internal validation in the studies used in this thesis, the data has been compared to other sections of the data using constant comparative method and checked that different perspectives are not ignored or forced upon. To verify, external validation of data, triangulation of sources was partly use, comparing interview data with data from observations. The benefits of using both observations and interviews as data sources include the verification of data validation through triangulation by comparing interview data with data from observations.

The focus of Paper I was to explore the practice of EBP in the PSG work process, how the PSG handled the various forms of evidence and values, how they came to collective agreement, and how they handled the practical tensions, i.e. negotiating and overcoming sometimes conflictual rationalities.

Reaching collective agreement involves a balancing act with enough structure and organization as a framework to enable the PSG members to use open deliberations. The process of coming to agreement was enhanced by the use of open deliberation, where PSG members were negotiating and making sense collectively. The goal of reaching agreement thus places value on individuals considering the good of the whole group, suggesting that all individuals were not always in agreement with the recommendations (priority gradings) and the fact that the PSG members felt the need for negotiations.

Group facilitation activities such as; practical exercises, the presence of a facilitator, a structured work process used as a framework for deliberation and the actual use of open discussion, were identified as important in reaching collective agreement.

Though the process of reaching collective agreement was characterized by collaboration rather than competition for the group´s support in the case study, their various, sometimes competing rationalities, were also in play. A scientific rationale clearly dominated how the priority gradings were arrived at in this medical setting, but making sense of the POs and the process of reaching priority gradings also involved aspects of norms and values as well as political conditions and aspects of power, i.e. struggle over arguments and positions.

The PSG consisted of many strong-willed people who "fought for their position" in the group with well-established expert knowledge, a need to negotiate, persuade and deliberate in order to reach agreement. One of the ways to handle the practical tensions was by using creative and collective new routines to deal with the situation. When the informants referred to their task, they often focused on the time consuming and frustrating process of "creating" POs, rather than just being involved with priority grading. There was a need to make sense together, to modify and create new POs. Avoiding deadlock in the discussions gives an apparent contrast to a rational model of decision-making, which commonly corresponds to the notion of EBP.

Thus, another important way to overcome deadlock was in activities whereby the members were paraphrasing as well as going back to the underlying evidence for the POs, in order to make sense of how to understand the data in different situations. Though evidence is never context-free and cannot easily be classified and weighted, it incorporates standpoints, assumptions, values and uncertainty, and always needs to be interpreted. If the proposal for a priority grading was not accepted in the "first" round of open deliberations, the discussion was continued into the "second" round after concerns had been raised by the group, or modifications had been made directly after the first round, resulting in new rounds of discussion. This allowed particularly difficult POs to take up the time they required.

Also, due to the lack of clear alternatives for comparison, it is implied that each and every PO was subjected to more or less lengthy discussions. The work process was thus both dynamic and iterative where a need for new POs was continuously discussed, and reaching agreement did not necessarily follow a linear process. Paper I reveals not only the uncertainty and ambiguity in working with EBP in practice but also how they *actually* moved forward. Therefore, uncertainty, ambiguity, and other values were also a distinguishing part of the process.

When the PSG had difficulty in reaching agreement on priority gradings, for example in situations when the overall evidence base was limited or when it was highly ambiguous regarding how to interpret the evidence, the use of cost-effectiveness data played an important role. It was used to avoid blocks in the PSG's deliberations in times of greater uncertainty and ambiguity, i.e. when concerns were being raised or there was a block in the open discussion. The use of cost-effectiveness data could therefore be regarded as a format for moving

the work process forward, and viewed as a "solution" to solving the task of making a recommendation.

Paper I thus shows the importance of having an awareness that people involved in policy processes do disagree, and also acknowledge their right to think differently in order to keep reflections, multiple interpretations and discussions alive. In the practice of EBP, in this case the work by PSGs, it is necessary to take into account the fact that disagreement is also a part of their task.

Paper II uses qualitative methodology to explore various themes on the use of cost-effectiveness data in priority gradings. It addresses themes related to the availability of cost-effectiveness data, understanding of the data, interpretation difficulties and reliance on the evidence. The paper concludes that cost-effectiveness data was accessed, in condensed text form and verbally, through the health economist present at the PSG meetings. The involvement of a health economist reinforced the notion that health economics was perceived as important throughout the group's work. The study supports the fact that healthcare decision makers at the national level have accepted the use of cost-effectiveness in their decision-making process.

In Paper II, examples were given of situations when cost-effectiveness impacted decisions taken and used in the PSG deliberations. Economic evidence should thus be viewed as part of the evidence-based knowledge "package". The use of cost-effectiveness data represented one of many factors that play a part in health policy decision-making. Cost-effectiveness data was lacking as decision support in the majority of cases, i.e. was not used. However, the priority gradings made by the PSG are based on the severity of the disease and clinical effectiveness as well as cost-effectiveness data. A consideration is that most informants had difficulty in isolating cost-effectiveness evidence, which represented a sub-component of the accumulated evidence base taken into account in decision-making.

Even if economic arguments are significant, research has shown that the expected benefits and risks of a treatment are the most important factors in making priority gradings [82]. Other studies have reported several important reasons for drug priority setting, and no single reason dominated in reaching a decision [83]. The findings verify the notion that cost-effectiveness data is not challenged to the same extent as clinical evidence and that greater weight is given to clinical effectiveness.

The research findings suggest that affordability was often seen as a pressing issue and, in that sense, has been associated with "something negative" prior to the work process. The term ´health economics´ had undergone a change and was now associated with a broader mind-set according to the informants, i.e. producing priority gradings by weighing evidence and including cost-effectiveness data. Instead, ethical considerations as well as general discussions were emphasised on what were considered "reasonable" investments.

The linear and simplistic goal of arriving at collective agreement is presented as an ideal for how to work with evidence-based policy (EBP). Though, there is a need to recognize the contextual elements in decision-making, and highlight institutional factors and incentives to employ use of cost-effectiveness analyses in decision-making [8]. In practice, all steps – when evidence is produced, when evidence-informed guidelines in the form of policy documents are produced and when these guidelines are interpreted and used in practice – involve negotiations and collective sense-making [30].

When the institutional considerations associated with incentives to employ economic evaluations [8], as mentioned in Chapter 1, are used as framework for the analysis, the results of Paper II show that the stated aims and goals were clearly stated, and there was a framework to organise the cost-effectiveness data. This would increase the PSG´s incentive to use the data in their decision-making according to the framework. The PSG were struggling to understand presented evidence which may have decreased the incentives to use cost-effectiveness data. The relationship to implementation was indirect as the priority gradings were not immediately binding on the national level and this would increase the incentives of use. The affiliations of the actors in the PSG may help to explain the predominant clinical-effectiveness used by the PSG members. The awareness of external scrutiny would also increase the incentives of use according to the framework. If the guidelines are to be implemented and be perceived as legitimate and fair, it is important for all the PSG members to stand by all the priority gradings made by the group. Institutional features of policy decision-making may thus provide a framework for the usage of economic evaluations.

Cost-effectiveness ratios or ICERs for the treatment of heart diseases, based on an extensive systematic literature search, were presented in Paper III. Available cost-effectiveness data represents an effort to amass cost-effectiveness

information in the form of a ranking or league table for different heart conditions and treatment strategies. The cost-effectiveness ranking or league table was not only compiled but also categorised according to the disease group areas. It was also summarised and broken down in order to convey as much information as possible to the reader in a simplified manner. Differentiating between patient groups with respect to low or high risk also gives important information, for example decision makers trying to optimise both the number of patients and the patients that might benefit from a treatment.

Cost-effectiveness ranking or league tables may thus provide a means of presenting cost-effectiveness evidence in terms of cost per QALY or LY gained. Using a generic outcome measure, such as QALYs, enables comparisons across different cost-effectiveness analyses. A methodological consideration was that both QALYs and LYs were included in the league table as outcome measures. The implication of this may be that the ICERs are overestimated, as the outcome measure LY was not adjusted. The cost-effectiveness analyses, using LY as the outcome measure, were included in the ranking or league table when the analyses were judged to be of high quality and no other analyses using QALYs as outcome measure were found. Several methodological considerations concerning ranking or league tables have been discussed in the introduction section of this thesis.

As stated earlier in the Materials and Methods chapter, only intervention strategies that are used in the Swedish healthcare system were included in the ranking or league tables. More than half of the results of the literature findings did not comply with the national guidelines and were therefore excluded. Thus, several intervention strategies found in the literature search were not included. As earlier accounted for, ICERs for the interventions included in the ranking or league tables were converted into SEK and adjusted to the 2009 price level. Ideally, cost-effectiveness analyses used in a Swedish setting should include Swedish unit costs. This would have been preferable. Due to both time and budget restriction, it was not feasible to adapt all cost-effectiveness analyses using Swedish unit costs for all of the hundreds of POs.

There is an increasing output of economic evaluations, which became apparent during the course of the literature search. Carrying out such an extensive literature search, covering the whole are of cardiovascular care, would probably not be feasible today. Identifying areas where evidence is lacking and decision

makers are in need of evidence as decision support would be a more feasible approach.

However, as noted in the above section, cost-effectiveness evidence needs to be both accessed and accepted by the decision maker in order to play a role in the decision-making process. Decision makers need evidence both in a condensed and extensive form. Cost-effectiveness ranking or league tables may thus provide valid information within a limited space, as decision support, aiding decision makers with the allocation of healthcare resources [84].

Paper IV provides an example of aiding decision makers in the introduction of a new medical technology. A decision-analytic modelling approach was used in Paper IV to assess the lifetime costs and effects of a new medical technology, catheter ablation (RFA), compared to AAD for patients with symptomatic AF. The purpose of economic evaluations is to offer guidance to decision makers and Paper IV provides an example of presenting them with evidence, in the form cost-effectiveness analysis, as decision support. The modelling approach provides a structure for the decision problem and was used as an analytic framework. Using a decision-analytic modelling approach implied that data from several sources might be used to populate the model with best available evidence. In this study, relevant randomised controlled trials, different published papers and Swedish register data were used as input variables for both treatment strategies. New parameter estimates can readily be incorporated into a model once more evidence becomes available. This is especially important when assessing novel medical technologies, such as the RFA treatment strategy.

Including relevant evidence may be considered consistent with the axioms of EBM, i.e. using evidence systematically and comprehensively in order to make clinical decisions [85]. Economic evaluations per se translate evidence into estimates of costs and effects, identifying the optimal option for resource allocation.

Using a decision-analytic modelling approach is appropriate in the absence of long-term clinical data, i.e. beyond the follow-up of clinical trials, which was the case in this study. In this study, a lifetime time horizon was used to analyse the RFA treatment strategy. A lifetime time horizon is relevant as benefits are likely to accrue well beyond the duration of a clinical trial and costs are largely the result of the initial intervention. The main costs for RFA treatment occur during

the first year due to considerably higher intervention costs compared to AAD treatment.

The RFA treatment strategy, when used as a second-line strategy, is now the standard procedure in Sweden and is in accordance with international clinical guidelines. AAD treatment involves the daily use of medications and is not always well tolerated by the patient. This is also a reason the RFA might be considered cost-effective compared to AAD. The AAD strategy has often proven unsuccessful, and the low efficacy AAD, therefore, favours the RFA treatment strategy. One could argue that the AAD treatment strategy might be associated with a higher disutility compared to the RFA treatment strategy. A methodological consideration was to use conservative estimates in order not to disfavour the AAD treatment strategy in the base-case analysis.

Considering that the RFA treatment strategy was new medical technology, several sources of uncertainty were taken into account when interpreting the results associated with methodological aspects and model assumptions. The use of probabilistic analysis allowed uncertain parameters to vary randomly within predefined distributions, reflecting the overall level of uncertainty of model parameters. Using a probabilistic modelling approach thus seemed appropriate to reflect this uncertainty. However, models based on short-term data always include an uncertainty regarding the long-term effects.

RFA treatment was associated with reduced cost and an incremental gain in QALYs and was considered a cost-effective treatment strategy compared to the AAD in a lifetime perspective. The two cost-effectiveness studies found, during the time of the analysis, confirmed the results of the study [86, 87]. The two key parameters found to be of most importance for examination were the reversion rates of the RFA procedure back to AF and variations in stroke risks in the different AF health states. These parameters have been discussed in the results section. Different annual reversion rates back to AF were considered in the alternative scenarios. A conservative estimate of the stroke risk was used in the base-case analysis for both the controlled and uncontrolled AF health states.

As concluded in Paper IV, follow-up studies would be important when confirming the sustainability of the RFA treatment strategy, i.e. whether the long-term benefits are maintained after the initial RFA procedure. Since the publication of Paper IV, a recent literature search revealed several studies on the long-term effects of the RFA treatment strategy [88-92], confirming the long-

term efficiency of RFA. Additionally, a cost-effectiveness analysis on the first-line treatment with RFA for patients with paroxysmal AF, was found [93]. The results show that first-line treatment with RFA is cost-effective for younger paroxysmal AF patients (< 50 years), based on the results from the MANTRA-PAF clinical trial. In older patients, AAD should be attempted before RFA.

An important implication of a decision-analytic modelling approach is that it provides a framework for decision-making, specifically under conditions of uncertainty. Modelling approaches provide flexibility, and through assessment of various types of uncertainty, they can identify priorities for future research. However, the results are always conditional on the data and structural assumptions of the model.

Future implications and conclusions

In health policy decision-making, in the case of the Swedish national guidelines, evidence-based knowledge is used to produce the guidelines. An important aspect of guidelines is that they should be based on current scientific research. Clinical scientific data, economic and ethical considerations influence the decision made. Economic evaluations may thus be viewed are a part of the evidence-based knowledge "package". Thus, the use of cost-effectiveness data represented one of many factors that played a role in health policy decision-making. The objective of all economic evaluations is to inform decision makers on the efficient allocation of scarce healthcare resources. Cost effectiveness data needs to be both accessed and accepted by the decision maker. Decision makers need evidence, both in extensive and condensed form. The ultimate goal of the national guidelines is to contribute towards patients receiving high-quality medical care and to support decisions on the efficient allocation of scarce healthcare resources. Thus, decision makers and politicians must make recommendations on how resources should be allocated. Certain medical conditions may be given higher priority gradings, i.e. given more resources than others, depending on the seriousness of the medical condition. This thesis contributes to the knowledge regarding how cost-effectiveness data is used in actual decision-making to ensure that the decisions are offered on equal terms and that patients receive medical care according to their needs so that they can attain maximum benefits.

- In the case of the national guidelines for heart diseases in Sweden, the PSG work process involved disagreement, and negotiations as part of their task.

- The written recommendations and guidelines, were arrived at to a large extent, by deliberation and also by creativity and included multiple interpretations and keeping discussions alive.

- Cost-effectiveness data was used when the overall evidence base was weak and when the PSG had trouble making priority gradings. Involvement of a health economist and dependence on data facilitated the use of data in the decision-making process. Economic arguments were used as a fine-tuning instrument and a counterweight for dichotomisation.

- Cost-effectiveness ranking or league tables constitute a way of presenting cost-effectiveness evidence thus aiding decision makers in providing valid information within a limited space. This helps decision makers to allocate healthcare resources appropriately. Moreover, a comprehensive compilation of health-economic evidence was made accessible for the treatment of heart diseases, which was useful in healthcare decision-making.

- The catheter ablation treatment (RFA) strategy was associated with reduced cost and an incremental gain in QALYs, and was thus considered a cost-effective treatment strategy. The analysis provides an example of the use of a decision-analytic modelling approach, offering decision makers guidance on the economically optimal course of action for specific decisions. The modelling approach provides an analytic framework for decision-making, specifically under conditions of uncertainty such as the introduction of new medical technology.

SUMMARY IN SWEDISH
(SAMMANFATTNING PÅ SVENSKA)

Hälsoekonomiska utvärderingar används för att informera beslutsfattare om en effektiv allokering av hälso- och sjukvårdens knappa resurser. Riktlinjer tas fram för att stödja beslut inom hälso- och sjukvården. Att producera riktlinjer är en komplex process och att inkludera hälsoekonomiska aspekter i de svenska nationella riktlinjerna som grund för prioriteringsbeslut särskiljer dem från dess europeiska motsvarigheter. Trots en ökad användning av att kostnadseffektanalyser i beslutsfattande, finns lite kännedom över det faktiska användandet. Den här avhandlingen tar upp frågor rörande den roll hälsoekonomiska utvärderingar spelar i hälso- och sjukvårdens besluts-fattande. Avhandlingen innehåller fyra delstudier som alla baseras på de svenska nationella riktlinjerna för hjärtsjukvård. De nationella riktlinjerna är en av de mest betydande exempel i Sverige som följer idén om evidensbaserad policy (EBP) i syfte att informera explicita prioriteringsbeslut.

Både delstudie I och II använder kvalitativ metod som studiedesign och baserades på samma empiriska datamaterial. Delstudie 1 utforskar hur beslutsfattare i en specifik arbetsgrupp, prioriteringsgruppen (PSG), hanterade olika former av evidens och värderingar, när de producerade de nationella riktlinjerna. Två huvudteman identifierades för att komma fram till rangordningsbeslut. Arbetsprocessen involverade motsättningar och förhandlingar som del av uppdraget. Delstudie I bidrar med en teoretisk och praktisk debatt om EBP. Delstudie II fokuserade på användandet av kostnadseffektdata som beslutsstöd i PSGs arbetsprocess. Studien adresserar vilken evidens som är tillgänglig, svårigheter med förståelse och tolkning, och tillit till evidens. Tre teman identifierades. Delstudie 1 bidrar med kunskap om hur kostnadseffektanalyser användes i faktiskt beslutsfattande. Användandet av kostnadseffektdata var en av många verktyg för att undvika blockering i diskussionen och för att komma fram till ett rangordningsbeslut. när det övergripande evidensunderlaget var svagt, vid osäkerhet och vid införandet av ny dyr medicinsk teknologi.

Kvantitativ metod användes för både delstudie III och IV. Delstudie III utforskar hur PSG presenterades med hälsoekonomiskt evidensunderlag som grund för sina rangordningsbeslut. Kostnadseffektkvoter för hjärtsjukdomar, baserade på en systematisk litteratursökning, presenterades och även hur dessa

resultat kan förmedlas och kommuniceras till beslutsfattare. Genom att använda en hälsoekonomisk ligatabell, hälsoekonomiskt evidensunderlag ge valid information inom ett begränsat utrymme, för att stödja beslutsfattare vid resursallokering inom hälso- och sjukvården. Avhandlingen innehåller även beslutsstöd i form av en hälsoekonomisk analys för kateterburen ablationsbehandling av förmaksflimmerpatienter. Delstudie IV utgör ett exempel på hur evidens kan presenteras, genom att använda beslutsmodellering som metod. Beslutsmodellering utgör ett analytiskt ramverk för beslutsfattande, specifikt under osäkerhet såsom vid införandet av en ny medicinsk teknologi. Resultaten visar att metoden förknippades med minskade kostnader och inkrementell ökning av kvalitetsjusterade levnadsår (QALYs) och ansågs vara en kostnadseffektiv behandlingsmetod i jämförelse med läkemedelsbehandling utifrån ett livstidperspektiv.

APPENDICES

APPENDIX 1: INTERVIEW GUIDE

TOPIC GUIDE

Introductory questions:

The interviewee´s background?

How did you come in contact with the priority setting group (PSG) for the first time?

Could you describe in your own words your view/perception of the task of the PSG?
- Immediate reactions to the task?
- Opinion of the task?

How would you describe the work process?
- What did you do?

The role of health economics:

What *type* of information (decision support) did you have access to during the priority setting process?
- Was there *sufficient* information (any information lacking)?
- Was it based on evidence?
- Other types of information/evidence (did you seek your own information)?
- Could you briefly comment on the health-economic facts document?
  Was there *balance* between the different parts (clinical and health economic, dominated/good/bad/problematic)
- Did the "box" correspond to the facts document (clinical and health-economic evidence, was there more?)

What is the reason behind the health-economic "box"?
- Is there a need for the health-economic "box"? Could it be removed?
- Are the clinical facts boxes sufficient?
- How was the health-economic facts document used?
- Why is there not a "box" for ethics?
- Higher status for health economics (compared to ethics)?
- Faith placed in the health-economic field?

Do you remember how health-economic arguments were used in the priority gradings?
- Could you give examples of arguments used (from a health-economic perspective)?
- When health-economic evidence was missing for example?
- When the evidence was not used?

How did the group reason in different controversial cases? Could you give examples of "tricky" cases?

- Example CASE 1 "Ablation"
- Example CASE 1 "Clopidogrel"
- Example CASE 1 "Maze"
- Example CASE 1 "ICD-CRT"
- How did you discuss differences in opinion?

Did you experience any problems in converting the health-economic evidence into priority gradings? What could have caused this?
- Did you have an understanding of the field?
- Interpretation difficulties?
- Inconsistencies: Similar health-economic evidence but different gradings?

Social context:

The group
- Did the group consist of a representative sample of people?
- Were there only specialists in the group?
- What section of cardiovascular care was represented?

Chairperson
- Did this work well/badly? Why?

How would you describe the process?
- What did you do?
- Did the process work well/badly? Why?

What "rules" applied?
- What happened if you were of a different opinion?

Other:

Would you like to add anything further?

APPENDIX 2: Cost-effectiveness ranking or league tables for acute coronary artery disease, stable angina, arrhythmias, heart failure and congenital heart disease in Euro (2009).

Acute Coronary Artery Disease

Intervention and compared intervention strategy	Patient group	ICER (Euro) per QALY or LY gained	Country	References
PCI and Glycoprotein IIb/IIIa receptor antagonist (abciximab) vs. no abciximab for the treatment of coronary heart disease	All patients	< 0 /QALY	UK	Vella [74] (2003)
Primary PCI vs. thrombolysis for acute myocardial infarction	All patients	< 0 /QALY	US	Lieu et al. [75] (1997)
SPECT imaging and coronary angiography vs. exercise electrocardiography and coronary angiography for the diagnosis of coronary artery disease	Women, age 60 years	<0 /QALY	UK	Mowatt et al. [76] (2004)
Primary PCI vs. thrombolytic therapy for acute myocardial infarction (STEMI)	All patients	< 0 /LY	Norway	Selmer et al. [77] (2005)
Statin (fluvastatin) vs. no statin treatment after PCI	LIPS, patients with diabetes	100 /QALY	UK	Scuffham et al. [78] (2005)
Clopidogrel and ASA vs. standard treatment (ASA) in patients with acute coronary syndromes	CURE	910 /LY	Sweden	Lindgren et al. [79] (2004)

Intervention	Population	Cost	Country	Reference
ACE inhibitor (trandolapril) vs. placebo after myocardial infarction	All patients (TRACE)	1 420 /LY	France	LePen et al. [80] (1998)
ACE inhibitor (ramipril) vs. placebo for heart failure after acute myocardial infarction, 3.8 year treatment	AIRE	1 620 /LY	Sweden	Erhardt et al. [81] (1997)
Statin (simvastatin) vs. placebo for the treatment of coronary heart disease	Men, direct and indirect costs	1 720 /LY	Sweden	Johannesson et al. [82] (1997)
ACE inhibitor (ramipril) vs. placebo for heart failure after acute myocardial infarction, 2 year treatment	AIRE	2 020 /LY	Sweden	Erhardt et al. [81] (1997)
Early invasive strategy vs. medical treatment in patients with unstable coronary artery disease	FRISC II	2 330 /QALY	Sweden	Janzon et al. [83] (2003)
PCI and glycoprotein IIb/IIIa receptor antagonist (abciximab) vs. no abciximab for the treatment of coronary heart disease	All patients	2 930 /LY	US	Kereiakes et al. [84] (2000)
Thrombolysis (streptokinase) vs. ASA for acute myocardial infarction < 4 hours after symptom onset	Age 65 years	3 030 /QALY	Ireland	Kellett [85] (1996)
ACE inhibitor (ramipril) vs. placebo for heart failure after acute myocardial infarction, 1 year treatment	AIRE	3 740 /LY	Sweden	Erhardt et al. [81] (1997)
ACE inhibitor (captopril) vs. placebo after myocardial infarction	Age 80 years, no survival benefit beyond 4 years	4 350 /QALY	US	Tsevat et al. [86] (1995)
Glycoprotein IIb/IIIa receptor antagonist (abciximab) vs. placebo after PCI	EPIC, high risk patients	4 450 /LY	Australia	Aristides et al. [87] (1998)

Intervention	Details	Cost	Country	Reference
ACE inhibitor (captopril) vs. placebo after myocardial infarction	Age 80 years, difference in survival benefit beyond 4 years	4 450 /QALY	US	Tsevat et al. [86] (1995)
ACE inhibitor (ramipril) vs. placebo for patients with coronary artery disease	HOPE	4 550 /LY	UK	Malik et al. [88] (2001)
Statin (fluvastatin) vs. no statin following successful first PCI	LIPS	4 960 /QALY	UK	Scuffham et al. [89] (2004)
ACE inhibitor (captopril) vs. placebo after myocardial infarction	Age 70 years, difference in survival benefit beyond 4 years	5 160 /QALY	US	Tsevat et al. [86] (1995)
Statin (simvastatin) vs. placebo for the treatment of coronary artery disease	Women, direct and indirect costs	5 360 /LY	Sweden	Johannesson et al. [82] (1997)
Statin (simvastatin) vs. placebo for the treatment of coronary artery disease	Men, direct costs	5 560 /LY	Sweden	Johannesson et al. [82] (1997)
ACE inhibitor (captopril) vs. placebo after myocardial infarction	Age 70 years, no survival benefit beyond 4 years	5 870 /QALY	US	Tsevat et al. [86] (1995)
Thrombolysis (streptokinase) vs. ASA for acute myocardial infarction < 4 hours after symptom onset	Age 80 years	6 270 /QALY	Ireland	Kellet [85] (1996)
ACE inhibitor (captopril) vs. placebo after myocardial infarction	Age 60 years, difference in survival benefit beyond 4 years	6 780 /QALY	US	Tsevat et al. [86] (1995)

Intervention	Population	Ratio	Country	Reference
Thrombolysis (t-PA) vs. ASA for acute myocardial infarction < 4 hours after symptom onset	Age 65 years	6 880 /QALY	Ireland	Kellet [85] (1996)
Clopidogrel vs. placebo in patients with acute coronary syndromes	CURE	7 280 /LY	US	Weintraub et al. [90] (2005)
Statin (pravastatin) vs. placebo in patients with established ischeamic heart disease	LIPID	7 890 /LY	Australia	Glasziou et al. [91] (2002)
Clopidogrel during 12 months vs. 6 months for acute coronary syndromes	CURE	7 990 /QALY	UK	Main et al. [92] (2004)
Thrombolysis (streptokinase) vs. ASA for acute myocardial infarction < 4 hours after symptom onset	Age 50 years	8 090 /QALY	Ireland	Kellett [85] (1996)
Glycoprotein IIb/IIIa receptor antagonist (GPA) vs. no GPA for patients with non ST elevation acute coronary syndromes	All patients	8 290 /QALY	UK	Palmer et al. [93] (2005)
Clopidogrel during 12 months vs. standard treatment for acute coronary syndromes	CURE	9 410 /QALY	UK	Main et al. [92] (2004)
Thrombolysis (t-PA) vs. ASA for acute myocardial infarction < 4 hours after symptom onset	Age 80 years	9 410 /QALY	Ireland	Kellet [85] (1996)
Statin (pravastatin) vs. placebo after myocardial infarction	CARE, ≥ age 60 years	9 510 /QALY	US	Tsevat et al. [94] (2001)
ASA vs. no treatment for the secondary prevention of coronary heart disease	All patients	10 420 /QALY	US	Gaspoz et al. [95] (2002)
ACE inhibitor (captopril) vs. placebo after myocardial infarction	Age 60 years, no survival benefit beyond 4 years	10 820 /QALY	US	Tsevat et al. [86] (1995)

Intervention	Subgroup	Cost	Country	Reference
Clopidogrel during 6 months vs. 3 months for acute coronary syndromes	CURE	11 430 /QALY	UK	Main et al. [92] (2004)
Glycoprotein IIb/IIIa receptor antagonist (eptifibatide) vs. placebo for the treatment of acute coronary syndromes	PURSUIT	11 430 /LY	Germany	Brown et al. [96] (2002)
Early invasive vs. conservative strategy for the treatment of unstable angina and non-ST elevation myocardial infarction	TACTICS-TIMI	12 040 /LY	US	Mahoney et al. [97] (2002)
Thrombolysis (alteplase) vs. streptokinase for the treatment of acute myocardial infarction	All patients	12 140 /QALY	UK	Boland et al. [98] (2003)
Thrombolysis vs. non-thrombolysis for acute myocardial infarction	Time to treatment, 0–6 h	12 440 /LY	US	Castillo et al. [99] (1997)
ACE inhibitor (captopril) vs. placebo after myocardial infarction	Age 50 years, difference in survival benefit beyond 4 years	12 540 /QALY	US	Tsevat et al. [86] (1995)
Thrombolysis (t-PA) vs. thrombolysis (streptokinase) for acute myocardial infarction < 4 hours after symptom onset	Age 65 years	12 950 /QALY	Ireland	Kellet [85] (1996)
Primary PCI vs. non-thrombolysis for acute myocardial infarction	All patients	13 350 /QALY	US	Lieu et al. [75] (1997)
SPECT imaging and coronary angiography vs. exercise electrocardiography and coronary angiography for the diagnosis of coronary artery disease	Age 60 years	13 450 /QALY	UK	Mowatt et al. [76] (2004)
Glycoprotein IIb/IIIa receptor antagonist (abciximab) in patients undergoing PCI vs. no abciximab	Patients with acute myocardial infarction	13 660 /LY	US	McCollam et al. [100] (2003)

Intervention	Subgroup	Ratio	Country	Reference
Clopidogrel plus ASA vs. ASA alone for the treatment of coronary artery disease	CURE, high risk patients	14 570 /QALY	US	Schleinitz et al. [101] (2005)
Thrombolysis (reteplase) vs. streptokinase for the treatment of acute myocardial infarction	All patients	14 670 /QALY	UK	Boland et al. [98] (2003)
Thrombolysis (t-PA) vs. thrombolysis (streptokinase) for acute myocardial infarction < 4 hours after symptom onset	Age 80 years	15 070 /QALY	Ireland	Kellett [85] (1996)
Thrombolysis vs. non-thrombolysis for acute myocardial infarction	All patients	15 170 /LY	US	Castillo et al. [99] (1997)
Thrombolysis (tenecteplase) vs. streptokinase for the treatment of acute myocardial infarction	All patients	15 880 /QALY	UK	Boland et al. [98] (2003)
Thrombolysis vs. non-thrombolysis for acute myocardial infarction	Time to treatment, 7–12 h	18 310 /LY	US	Castillo et al. [99] (1997)
Glycoprotein IIb/IIIa receptor antagonist (eptifibatide) vs. placebo in patients with non ST-elevation acute coronary syndromes	PURSUIT	20 530 /QALY	US	Mark et al. [102] (2000)
Thrombolysis (t-PA) vs. ASA for acute myocardial infarction < 4 hours after symptom onset	Age 50 years	20 740 /QALY	Ireland	Kellett [85] (1996)
Glycoprotein IIb/IIIa receptor antagonist (abciximab) vs. no abciximab for the treatment of acute myocardial infarction with PCI	CADILLAC	23 770 /QALY	US	Bakhai et al. [103] (2003)
Clopidogrel for patients not eligible for ASA (ASA intolerance) vs. no treatment for secondary prevention of coronary heart disease	Patients with ASA intolerance	29 230 /QALY	US	Gaspoz et al. [95] (2002)

Intervention	Subgroup	Ratio	Country	Reference
Physical exercise-based rehabilitation vs. conventional treatment for secondary prevention after an acute coronary event	All patients	30 650 /QALY	Australia	Briffa et al. [104] (2005)
Statin (pravastatin) vs. placebo after myocardial infarction	CARE	32 270 /QALY	US	Tsevat et al. [94] (2001)
Thrombolysis (t-PA) vs. thrombolysis (streptokinase) for acute myocardial infarction	GUSTO	40 360 /LY	US	Mark et al. [105] (1995)
Thrombolysis (t-PA) vs. thrombolysis (streptokinase) for acute myocardial infarction < 4 hours after symptom onset	Age 50 years	40 970 /QALY	Ireland	Kellett [85] (1996)
Thrombolysis (t-PA) vs. thrombolysis (streptokinase) for acute myocardial infarction	GUSTO, inferior myocardial infarction, ≤ age 40 years	226 180 /LY	US	Mark et al. [105] (1995)

Stable Angina

Intervention and compared intervention strategy	Patient group	ICER (Euro) per QALY or LY gained	Country	References
CABG vs. PCI for patients with multivessel coronary disease	BARI, patients with diabetes	<0 /LY	US	Hlatky et al. [106] (1997)
Exercise echocardiography vs. exercise electrocardiography for the diagnosis of suspected or known coronary artery disease	All patients	2 430 /LY	US	Marwick et al. [107] (2003)
Clopidogrel and ASA (12 months) vs. clopidogrel and ASA (28 days) following PCI	CREDO	3 030 /QALY	Sweden	Ringborg et al. [108] (2005)
Stent plus glycoproteinIIb/IIIa receptor antagonist (abciximab) vs. PCI plus abciximab	EPISTENT	5 360 /LY	US	Topol et al. [109] (1999)
Clopidogrel vs. placebo for patients after PCI	CREDO	6 580 /LY	US	Beinart et al. [110] (2005)
Clopidogrel plus ASA vs. ASA alone in patients with unstable coronary artery disease undergoing PCI	PCI-CURE	7 490 /LY	Sweden	Lindgren et al. [111] (2005)
Stent vs. no stent for the treatment of coronary artery heart disease with PCI	New patients	9 310 /QALY	UK	Vella [74] (2003)
CABG vs. PCI for the treatment of multivessel coronary artery disease	BARI	12 640 /LY	US	Hlatky et al. [112] (1997)
Prolonged treatment (1 month-12 months) with Clopidogrel vs. no treatment after PCI	CREDO	14 770 /LY	US	Cowper et al. [113] (2005)
Exercise echocardiography vs. SPECT imaging in patients with stable chest	Patients with annual risk of cardiac death or myocardial infarction (MI) < 0.02	19 420 /LY	US	Shaw et al. [114] (2006)
CABG vs. PCI among coronary disease patients appropriate for	All patients	27 010 /QALY	UK	Griffin et al. [115] (2007)

CABG only

Intervention	Population		Country	Reference
CABG vs. PCI for patients with ≥ 2 vessel coronary disease or > 50 % stenosis	BARI	27 510 /LY	US	Hlatky et al. [106] (1997)
SPECT imaging vs.exercise echocardiography in patients with stable chest pain	Patients with established coronary disease	30 550 /LY	US	Shaw et al. [114] (2006)
Exercise echocardiography vs. SPECT imaging in patients with stable chest pain	Patients with intermediate risk Duke Treadmill score (>−11 and <4)	37 230 /LY	US	Shaw et al. [114] (2006)
Exercise echocardiography vs. exercise electrocardiography for the diagnosis of chest pain	Men, age 55, typical angina	43 600 /QALY	US	Kuntz et al. [116] (1999)
Exercise echocardiography vs. SPECT imaging in patients with stable chest pain	All patients	68 080 /LY	US	Shaw et al. [114] (2006)
Screening with computor tomography vs. Framingham risk index alone to identify patients at risk for coronary artery disease	Age 39–45 years	81 830 /QALY	US	O'Malley et al. [117] (2004)
Whole-body computor tomography screening vs. no screening for asymptomatic 50-year old men	All patients	142 330 /LY	US	Beinfeld et al. [118] (2005)
Exercise echocardiography vs. SPECT imaging in patients with stable chest pain	Patients with annual risk of cardiac death or myocardial infarction (MI) > 0.02	324 610 /LY	US	Shaw et al. [114] (2006)
Drug eluting stents (DES) vs. conventional stents for patients with coronary artery disease undergoing PCI	Patients with diabetes	517 820 /QALY	UK	NICE [119] (2007)
Drug eluting stents (DES) vs. conventional stents for patients with coronary artery disease undergoing PCI	All patients	619 880 /QALY	UK	NICE [119] (2007)
PCI vs. CABG among coronary disease patients appropriate for CABG only	All patients	∞ /QALY	UK	Griffin et al. [115] (2007)

Arrhythmias

Intervention and compared intervention strategy	Patient group	ICER, Euro per QALY or LY gained	Country	References
Rate control (medical treatment) vs. rhythm control for the treatment of persistent atrial fibrillation	RACE	<0 /event avoided	Netherlands	Hagens et al. [120] (2004)
Initial radiofrequency ablation vs. episodic medical management for supraventricular tachycardia	All patients	< 0/QALY	US	Cheng et al. [121] (2000)
Initial radiofrequency ablation vs. long-term medical management supraventricular tachycardia	All patients	< 0 /QALY	US	Cheng et al. [121] (2000)
Warfarin vs. ASA for patients with atrial fibrillation	Patients with high stroke risk	< 0 /QALY	US	Gage et al. [122] (1995)
Warfarin vs. no prophylaxis for patients with atrial fibrillation	Patients with high stroke risk	< 0 /QALY	US	Sullivan et al. [123] (2006)
ICD vs. no ICD for prevention of sudden death in young people with inherited cardiac arrhythmias	Men with LQTS	3 140 /QALY	US	Goldenberg et al. [124] (2005)
Dual chamber pacing vs. ventricular pacing for patients with sick sinus syndrome	MOST	6 370 /QALY	US	Rinfret et al. [125] (2005)
ICD vs. no ICD for prevention of sudden death in young people with inherited cardiac arrhythmias	Women with LQTS	6 680 /QALY	US	Goldenberg et al. [124] (2005)
Warfarin vs. ASA for patients with atrial fibrillation	Patients with moderate stroke risk	9 100 /QALY	US	Gage et al. [122] (1995)
Dual chamber pacing vs. single chamber ventricular pacing for patients with bradycardia due to AV-block	All patients	12 950 /QALY	UK	Castelnuovo et al. [126] (2005)
Dual chamber pacing vs. single chamber ventricular pacing for patients with bradycardia due to sick sinus syndrome	All patients	14 570 /QALY	UK	Castelnuovo et al. [126] (2005)
ICD vs. no ICD for prevention of sudden death in young people with inherited cardiac arrhythmias	Women with hypertrophic	16 490 /QALY	US	Goldenberg et al. [124] (2005)

Intervention		Cost-effectiveness	Country	Reference
	cardiomyopathy			
ICD vs. no ICD for prevention of sudden death in young people with inherited cardiac arrhythmias	Men med hypertrophic cardiomyopathy	16 890 /QALY	US	Goldenberg et al. [124] (2005)
ICD vs. antiarrhythmic drug treatment (amiodarone) for patients with arrhythmias	High risk patients	33 890 /QALY	US	Owens et al. [127] (2002)
ICD vs. antiarrhythmic drug treatment used as secondary prevention for arrhythmias	Patients having survived a cardiac arrest, LVEF<0.35	38 440 /QALY	UK	NICE [128] (2006)
CRT-ICD vs. medical treatment alone for patients with heart failure	COMPANION	40 560 /QALY	US	Feldman et al. [129] (2005)
ICD vs. conventional medical treatment for patients with a history of myocardial infarction (MI)	MADIT II, EF<0.3	47 640 /LY	US	Al-Khatib et al. [130] (2005)
ICD vs. conventional treatment for patients after myocardial infarction (MI)	MADIT II, EF<0.3	47 950 /QALY	US	Sanders et al. [131] (2004)
ICD vs. control treatment for patients after myocardial infarction (MI)	MADIT II, EF<0.3	50 980 /QALY	US	Sanders et al. [132] (2005)
ICD vs. antiarrhythmic drug treatment (amiodarone) for patients with arrhthmias	Moderate risk patients	51 590 /QALY	US	Owens et al. [127] (2002)
ICD vs. medical treatment for patients with chronic heart failure	SCD-HeFT, patients with NYHA II or III	55 230 /LY	US	Mark et al. [133] (2006)
CRT with ICD vs. CRT alone for patients with heart failure	CARE-HF, battery life 5 years	59 990 /QALY	UK	Yao et al. [134] (2007)
ICD vs. antiarrhythmic drug treatment for the treatment of ventricular tachyarrhythmias	Patients with severe ventricular tachycardia	62 820 /LY	US	Larsen et al. [135] (2002)
ICD vs. conventional medical treatment for patients after myocardial infarction (MI)	MADIT II, EF<0.3	86 290 /LY	US	Zwanziger et al. [136] (2006)
ICD vs. conventional medical treatment for congestive heart failure (sudden death prevention)	Patients with NYHA II or III	92 250 /QALY	US	Chen et al. [137](2004)

ICD vs. antiarrhythmic drug treatment (amiodarone) for patients with arrhythmias	Low risk patients	109 350 /QALY	US	Owens et al. [127] (2002)
CRT-ICD vs. CRT alone for patients with heart failure	COMPANION	169 030 /QALY	US	Feldman et al. [129] (2005)
Dual chamber pacing vs. single chamber atrial pacing for patients with bradycardia due to sick sinus syndrome	All patients	∞ /QALY	UK	Castelnuovo et al. [126] (2005)
Screening of young active athletes vs. no screening for sudden death prevention	Age 12 years	∞ /QALY	Sweden	Brodtkorb [138] (2006)

Heart Failure

Intervention and compared intervention strategy	Patient group	ICER (Euro) per QALY or LY gained	Country	References
Aldactone (spironolactone) vs. placebo for the treatment of severe heart failure	RALES, high risk patients	<0 /QALY	US	Glick et al. [139] (2002)
BNP vs. echocardiography as a screening test for heart failure	Breathless patients	< 0 /event avoided	UK	Sim et al. [140] (2003)
ARB (candesartan) vs. placebo for patients with heart failure	CHARM-Added, NYHA II-IV, LVEF <0.40	< 0 /LY	UK	McMurray et al. [141] (2006)
Beta blockade (metoprolol) vs. placebo for the treatment of heart failure	All patients	2 630 /LY	US	Gregory et al. [142] (2001)
Beta blockade (bisoprolol) vs. placebo for the treatment of heart failure	All patients	3 540 /LY	US	Gregory et al. [142] (2001)
Beta blockade (carvedilol) vs. placebo for the treatment of heart failure	All patients	7 080 /LY	US	Gregory et al. [142] (2001)
CRT in combination with optimal medical treatment vs. medical treatment alone for patients with heart failure	COMPANION	18 410 /QALY	US	Feldman et al. [129] (2005)
CRT plus medical treatment vs. medical treatment alone for patients with severe heart failure	CARE-HF, NYHA III-IV, LVEF<0.35	19 420 /QALY	UK	Calvert et al. [143] (2005)
Screening with BNP plus echocardiography vs. no screening to identify asymptomatic patients with heart failure	Men, age 60	21 040 /QALY	US	Heidenreich et al. [144] (2004)
Beta blockade (carvedilol) vs. placebo for the treatment of heart failure	The US Carvedilol Heart Failure Trials Program	29 840 /LY	US	Delea et al. [145] (1999)
CRT plus medical treatment vs. medical treatment alone for	Patients with NYHA III	34 490 /QALY	Germany	Banz [146] (2005)

patients with heart failure	or IV			
Screening with echocardiography vs. no screening to identify asymptomatic patients with heart failure	Men, age 60	53 210 /QALY	US	Heidenreich et al. [144] (2004)
Screening med BNP plus echocardiography vs. no screening to identify asymptomatic patients with heart failure	Women, age 60	72 830 /QALY	US	Heidenreich et al. [144] (2004)
Screening BNP vs. no screening to identify asymptomatic patients with heart failure	Men, age 60	85 170 /QALY	US	Heidenreich et al. [144] (2004)
CRT vs. medical treatment for patients with symptomatic heart failure	Patients with reduced ventricular function	99 130 /QALY	US	Nichol et al. [147] (2004)
Left ventricular assist device (LVAD) used as bridge for heart transplantation vs. medical treatment for end-stage heart failure	Patients on the heart transplantation waiting list	99 330 /QALY	UK	Clegg et al. [148] (2005)
Left ventricular assist device (LVAD) used as long-term chronic support vs. medical treatment for end-stage heart failure	Patients excluded from the heart transplantation waiting list	259 870 /QALY	UK	Clegg et al. [148] (2005)
Screening with echocardiography vs. no screening to identify asymptomatic patients with heart failure	Women, age 60	447 710 /QALY	US	Heidenreich et al. [144] (2004)
Screening with BNP vs. no screening to identify asymptomatic patients with heart failure	Women, age 60	958 040 /QALY	US	Heidenreich et al. [144] (2004)

Congenital Heart Disease

Intervention and compared intervention strategy	Patient group	ICER (Euro) per QALY or LY gained	Country	References
Antibiotic prophylaxis (clarithromycin) vs. no treatment for patients undergoing dental procedures	Patients with increased risk for endocarditis	82 950 /QALY	US	Agha et al. [149] (2005)
Antibiotic prophylaxis (cephalexin) vs. no treatment for patients undergoing dental procedures	Patients with increased risk for endocarditis	93 130 /QALY	US	Agha et al. [149] (2005)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, Acetylsalicylic Acid (aspirin); BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CRT, cardiac resynchronisation therapy; Dominant (<0), a treatment strategy associated with incremental gain in effects with reduced costs; EF, ejection fraction; ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; LQTS, long QT syndrome; LVEF, left ventricular ejection fraction; LY, life year; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; QALY, quality adjusted life year; SPECT, single-photon emission computed tomography

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