Economic Evaluation of Diagnostic Strategies for Atrial Fibrillation:

A Markov model for the Netherlands

ERASMUS UNIVERSITY ROTTERDAM

Erasmus School of Economics

Department of Economics

Abstract

The health care market is characterised by many market imperfections. Cost-effectiveness analyses aim to replicate consumption decisions to optimally allocate resources. This paper compares the cost effectiveness of the current diagnostic strategy for atrial fibrillation (AF) to diagnostic strategies based on the relatively new Stroke Risk Analysis (SRA), from a health care sector perspective. The cost-effectiveness analysis is conducted by a Markov model, a mathematical simulation model to calculate the costs and health effects in terms of quality-adjusted life years (QALYs) of each diagnostic strategy for a targeted population aged 65 and older with AF symptoms. The comparative analyses result in incremental costs and incremental QALYs of the SRA strategies compared to care as usual. AF patients have an increased risk of stroke that can be mitigated with treatment once they are diagnosed. The simulation model demonstrates that the SRA strategies increase AF diagnoses but do not increase the quality-adjusted life years of the target population, compared to care as usual. The health benefits of avoided strokes in newly diagnosed AF patients are outweighed by the negative health effects due to treatment complications in newly, correctly and incorrectly, diagnosed individuals.

Supervisor: Anne Gielen

Name: Vera Baaij

Student number: 343915

Email address: vbaaij@gmail.com

Table of Contents

List of Abbreviations

AF	Atrial fibrillation
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
ECG	Electrocardiogram
EMR	Electronic medical record
GP	General practitioner
HTA	Health Technology Assessment
NICE	National Institute for Health and Care Excellence
PE	Physical examination
SRA	Stroke Risk Analysis
QALY	Quality-adjusted life year
WHO	World Health Organization
WTP	Willingness to pay

1. Introduction

With aging populations in many developed and developing countries, cerebrovascular events, better known as strokes, are becoming an increasingly important issue to address (Camm et al., 2010; Fuster et al., 2011; Naccarelli, Varker, Lin, & Schulman, 2009). According to the World Health Organization (WHO) strokes kill approximately 5.7 million people annually worldwide (Mackay & Mensah, 2004). Strokes also impose an economic burden because it leads to high health care costs, directly after the event and indirectly due to the care needed in the years after the event. Strokes are increasingly occurring at a younger age, due to which the average costs per patient of aftercare increase, as well as costs related to work absence (Camm et al., 2010).

Atrial fibrillation (AF) is a condition characterised by an abnormal heart rhythm, a cardiac arrhythmia. It multiplies the risk of stroke by a factor of five and is the cause of about 20 per cent of all strokes (Camm et al., 2010; Schaefer, Leussler, Rosin, Pittrow, & Hepp, 2014). Atrial fibrillation is difficult to diagnose because it is a condition that starts as paroxysmal, that is, the patient experiences a sudden abnormal heart rhythm alternated with a normal rhythm with unpredictable intervals. With traditional diagnostic tools, one of these unpredictable episodes has to be recorded during an electrocardiogram (ECG) before AF can be diagnosed. Therefore, there are many undiagnosed and untreated AF patients, that have an increased risk of stroke. Opposed to other causes of strokes, AF, once diagnosed, can be treated with anticoagulation therapy and reduce the risk of stroke by up to 64 per cent (Camm et al., 2010). Because of the increasing societal burden of strokes, it can be valuable to evaluate the alternative diagnostic strategies for AF. Health technologies are generally evaluated through a health technology assessment (HTA). This constitutes of the identification and prioritisation of technologies, followed by their assessment and review. The first priority is the assessment of the safety and efficacy. Once this has been demonstrated, ethically more difficult questions come into play. The economic impact of the technology and other possible consequences for society have to be assessed. Together, the results serve as the basis for the final stage of the HTA, the decision to implement a new technology by a public decision maker (Healy, Paul & Pugatch, 2009).

This paper assesses the economic impact of a health technology, by answering the following question: 'What is the most cost-effective strategy in terms of costs per quality-adjusted life year to diagnose AF?'. To answer this question, a cost-effectiveness analysis (CEA) is conducted by constructing a mathematical framework that simulates the use of three different diagnostic strategies for AF for a specific group of people. Through this framework, a Markov model, the costs per quality-adjusted life year (QALY) of each strategy are determined and compared to assess the cost effectiveness of the strategies. The use of a mathematical framework avoids the need for clinical trials with relatively high costs.

The main test of the current common diagnostic strategy is the Holter analysis. This is an ECG of 24 hours or longer that is analysed by a Holter analyst. This method requires the detection of an active episode, which can take up to several weeks. This strategy is compared to two other strategies with a Stroke Risk Analysis (SRA). This is a relatively new diagnostic tool, that applies an algorithm to an ECG to detect AF. The diagnostic strategies differ in terms of costs and in the ability to diagnose AF. Diagnosis is followed by treatment, which reduces the risk of strokes. This research adds to the literature of health economics by applying the methodology of mathematical modelling for cost-effectiveness analyses to the comparison of the current diagnostic strategy for AF with a new diagnostic tool.

The paper is organised as follows. The next chapter reviews the literature on the economic theory of cost-effectiveness analyses in the health care market. In chapter 3 the methodology of the model is discussed. It gives an overview of the diagnostic strategies, the health states, and the events that characterise the model. In the fourth chapter the results of the comparative analyses are presented. Chapter 5 concludes by combining the theoretical and empirical results, and with a discussion of the limitations of this research and recommendations for future research.

2. Literature review

There are different approaches to the economic evaluation of health technologies, or more generally medical interventions. Ideally, a clinical trial is conducted in which all costs and benefits are measured for a longer period of time. Apart from possible ethical obstacles to accurately compare different health technologies, clinical trials are

costly. It is no longer economically or practically feasible to conduct trials for all medical interventions because of the ever-increasing number of new interventions. Moreover, for an accurate evaluation it might be necessary to measure the long-term effects, such as over the lifetime of a target population. This would delay the implementation of new interventions by a long time. Because of these difficulties, alternative approaches of simulation modelling for the economic evaluation of health technologies have been developed (Meltzer & Smith, 2011). On the basis of literature and available data, a mathematical model can be construed to simulate the long-term costs and benefits of a medical intervention, such as a new health technology. This can be used to assess the cost effectiveness of the intervention. The difficulties of this approach include the correct prediction of human behaviour and making the correct assumptions and simplifications, but data availability probably forms the largest impediment. The benefits of simulation are, conditional upon data availability, the choice of any desirable time horizon and target population (Edlin, McCabe, Hulme, Hall, & Wright, 2015).

When the high informational demands are met, simulation modelling is a viable alternative for clinical trials for the purpose of economic evaluation of medical interventions, which is the approach that is adopted in this paper. Simulation modelling requires making assumptions on, for example, the scope and perspective of the analysis. For this purpose, it is helpful to start with the theoretical basis of the economic evaluation of medical interventions in general. The literature review starts with a discussion of the imperfections of the health care market, that form the rationale of the economic evaluation of medical interventions. Two types of analyses are proposed, cost-benefit analysis and cost-effectiveness analysis. The choice for the latter is explained by contrasting the welfarist and the extra-welfarist approach. The chapter concludes with a discussion of theoretical issues of CEAs.

2.1 Imperfections of Health Care Markets

Quantities and prices on health care markets are usually not determined by market forces. The demand side of the health care market, formed by patients, is characterised by imperfect information and a lack of choice, because of the dependence on the health care providers in consumption choices. The complexity of medicine and health care creates the conditions for a market in which the demand side

has to trust in the expertise of the supply side, the physicians, for the right consumption choices in for example diagnostic tools and treatment. The concept of trust, with physicians under a social obligation to act in the patient's best interest, was already recognised by Arrow in 1963, in his study of uncertainty in medical care. Another characteristic of the demand side of the health care market denoted by Arrow is the nature of demand for health care, which in large depends on the health of an individual at a specific moment (Arrow, 1963). Nowadays the demand for health care is usually seen as an average over the lifetime of a representative individual or of a group of individuals (Chandra, Cutler, & Song, 2011).

In most developed countries the majority of the population is insured for health care costs, to a certain extent. Therefore, the health care demand side can be distorted because of the moral hazard problem, which refers to the increase of the use of health care services when these are covered by insurance (Chandra et al., 2011; McGuire, 2011). Basic health care insurance then distorts the price signal for the demand for health care. However, additional health care insurance was not found to be explanatory for increases in health care spending in empirical research (Zuckerman, Waidmann, Berenson, & Hadley, 2010). Furthermore, the health care insurance market is characterised by asymmetric information, which gives rise to adverse selection problems (Pauly, 1974). Insurance companies do not have access to all information about the characteristics of their clients. With full information on these characteristics, insurers would charge a higher price to people with lesser health. When perfect discrimination between people with different qualities of health is not possible, adverse selection becomes an issue. This issue arises when people with lesser health, that are relatively costlier for the insurer, buy more health insurance compared to healthy people such that the price of the insurance increases. The higher price can drive healthy people out of the insurance market, because it is no longer profitable for them to buy health care insurance. This can further distort the demand for health care. When health care insurance is mandatory in a country, the adverse selection problem does not arise.

The consequences of asymmetric information and health care insurance discussed above lead to a lack of incentives to minimise costs by the demand side. On the supply side there are different reasons for suboptimal outcomes. Medical personnel

are not always perfect agents for their patients (Chandra et al., 2011). Physicians are both direct suppliers of services and products on the health care market, and agents for patients because they decide on treatment and diagnostic methods that are supplied by third parties. This principal-agent relationship can be affected by the physician's personal preferences, financial incentives and other biases, in addition to the patient's best interest. The extent to which these biases are relevant differs per area of medicine. So-called grey areas of medicine refer to areas where economic incentives are an important factor in treatment decisions, because there is little clinical guidance. In these areas, and to a lesser extent in areas where treatment decisions are based on authorative guidelines, much heterogeneity in treatment decisions is observed (Chandra et al., 2011; Feldstein, 2011). The previously discussed market imperfections on the demand side of imperfect information and the subsequent lack of incentives to minimise costs are other explanatory variables for this heterogeneity (Anthony et al., 2009). However, studies show that the heterogeneity in treatment choices is mostly caused by factors on the supply side (Campbell et al., 2007; Lucas, Sirovich, Gallagher, Siewers, & Wennberg, 2010; McClellan, 2011; Sommers et al., 2008). Other stakeholders such as governmental institutions, insurance companies and other providers of medical services stakeholders affect the incentives of the physicians on the supply side as well.

Together, the imperfections of the health care market create the need for cost-effectiveness measures. The demand side is likely to over-consume and does not have perfect information to make treatment decisions, and physicians on the supply side are not perfect agents for the demand side. Methods for the economic evaluation of medical interventions such as new health technologies were developed to replicate consumption decisions and optimally allocate resources (Meltzer & Smith, 2011). Alternatives are compared with the objective to optimise a welfare function under a budget constraint, a methodology with its foundation in the field of welfare economics.

2.2 Welfare Economics and the Economic Evaluation of Health Technologies

Welfare economics is concerned with collective wellbeing, for example the optimisation of a social welfare function. Welfare economics aims to provide a

coherent and ethical framework for the comparison of the social desirability of different states of the world (Boadway & Bruce, 1984).

The desirability of alternative states is assessed with the utility principle, which expresses that individuals are rational and make utility maximizing choices. In the framework of welfare economics, individuals can decide best on how to optimise their utility, which is derived from outcomes of choices. The characteristic that the desirability of a state of the world solely depends on the utility of the individuals involved is called welfarism. In the economic evaluation of health care decisions, this characteristic has been argued to be limiting, because the desirability of a state of the world depends on multiple factors (Brouwer, Culyer, van Exel, & Rutten, 2008).

Therefore, there are both economic evaluations of medical interventions that can be characterised as taking a welfarist or an extra-welfarist approach (Chandra et al., 2011). Brouwer et al. (2008) define welfarism by an initial normal distribution of wealth and income, where social welfare increases with a Pareto improvement, that is, a change that makes at least one individual better off without making other individuals worse off. For the welfarist approach individual utility is the only outcome, whereas an extra-welfarist approach can involve multiple and different outcomes. It broadens the definition of what can lead to welfare. Furthermore, the welfarist approach limits itself to the valuation of the objective variable by affected individuals, for which their preferences can be the only weighting factor. In the extra-welfarist approach outcomes can be weighed by other factors than the individual's preferences and it allows for comparisons of outcomes between different agents (Brouwer et al., 2008).

Cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA) are the most commonly used tools for the economic evaluation of medical interventions. A CBA compares costs and benefits, and inherently recommends the adoption of the alternative that is evaluated with positive net benefits (Garber & Phelps, 1997). The CBA method requires expressing all costs and health benefits explicitly in monetary units. Monetizing health benefits can be acceptable for economists, but is often met with scepticism by non-economists (Garber & Sculpher, 2011). Especially for politicians and other decision makers in the public field it can be a sensitive issue. There are different methods to express health benefits in monetary units, such as

questionnaires or information acquisition based on revealed preferences. In the translation of this information into monetary units, regardless of the method that is used, information can get lost or inaccurately depicted. Also, there are ethical objections to expressing health benefits, such as increased survival chances, in monetary units (Garber, Weinstein, Torrance, & Kamlet, 1996). The difficulties of using CBA in the health care domain led to the preference for cost-effectiveness analysis (CEA), both in the literature and in practice (Meltzer & Smith, 2012; Garber & Sculpher, 2012). CEAs can either take a welfarist or an extra-welfarist approach, depending on the definition and the conceptualisation of the objective function. It is considered advantageous that only health costs have to be expressed in monetary units in CEAs. Health benefits can be expressed in a non-monetary unit, for example in incremental life years obtained by the implementation of a medical intervention such as the use of a new health technology. However, as the next section will elaborate on, the CEA method rather differs in the manner of monetizing health benefits than in the ability to avoid it.

2.3 Cost-Effectiveness Analysis

The CEA method is the most widely used tool for economic evaluation in the health care domain and has been been developing for over 30 years (Drummond, O'Brien, Stoddart, Torrance, & Sculpher, 2005). The reasons for the emergence of CEAs explained in the previous section have strongly affected their methodology. As Meltzer and Smith (2011) explain, the need for a workable method, with feasible information requirements and less reliance on the monetary valuation of health, led to the development of CEAs in practice ahead of theory. This led to a set of practices that is not always coherent and consistent, but its increasingly widespread use gave rise to the need for comparable and non-biased analyses. The theory that emerged was an attempt to codify existing practices in a coherent manner. Methodological controversies continue to exist, and the methods for CEA are still being further developed and becoming more sophisticated (Meltzer & Smith, 2011). The economic theoretical basis that underpins the existing set of practices is discussed in subsection 2.3.1, followed by issues regarding the design of CEAs (subsection 2.3.2). The chapter concludes with decision making on the basis of CEAs (subsection 2.3.3).

2.3.1 Economic Theoretical Foundation

Cost-effectiveness analyses in the health care domain have by definition a multidisciplinary theoretical foundation. It combines clinical epidemiology for the incidence and prevalence of diseases, medicine for the diagnosis and treatment of diseases, and mathematics for modelling. The economic theoretical foundation is at the very essence of CEA, namely the objective to maximise welfare through efficient resource allocation when facing a decision problem. This finds its origins in welfare economics, but as discussed earlier it is also possible to take an extra-welfarist approaches, with an objective to maximise a different concept than individual or collective utility (Garber & Sculpher, 2011). The development of CEA in practice led to many different approaches to the perspective and the scope of analyses, because the design of each CEA is based on the needs of the decision maker in question (Meltzer & Smith, 2011). The commonality of CEAs of medical interventions is the objective to inform decision making based on economic efficiency. Ultimately, the CEA should demonstrate what the most efficient allocation of resources is through a comparative analysis of the costs and consequences of the alternatives (Drummond, O'Brien, Stoddart, Torrance, & Sculpher, 2005). This allows any CEA to be put in a conventional micro-economic framework of consumer choices under a budget constraint, regardless of the differences in scope and perspective. For example, Garber and Phelps (1997) use a Von Neumann-Morgenstern utility framework to discuss the underlying principles of CEA and its use for the economic evaluation of medical interventions. With the constant advancement of CEAs in theory and in practice, almost 15 years later Meltzer and Smith discuss CEA in a more general manner as a classic optimisation problem to assess the advancements and the controversies that continue to exist about CEAs of medical interventions. These mostly regard the design of the CEA, such as issues of scope and perspective. The underlying economic theory of the efficient allocation of resources to maximise health benefits remains the same. Simply put, CEA should determine the optimal quantity, for which the marginal costs equal the marginal benefits. After this point it is no longer profitable to increase the quantity because the extra costs exceed the incremental benefits. However, CEA is preferred over CBA exactly because the benefits do not have to be defined in monetary units. The benefits in CEAs are

expressed as utility, or another non-monetary concept of interest to the decision maker such as life years. Moreover, the optimal quantity to be determined, a medical intervention such as a new health technology, cannot always be varied continuously and can have a discrete or binary nature instead. Therefore, the optimal quantity cannot be determined by setting the incremental benefits equal to their incremental costs. Instead, the analysis ranks the different options according to their ratio of incremental costs to incremental benefits, for example according to the marginal costs per saved life year (Meltzer & Smith, 2011).

2.3.2 Design of Cost-Effectiveness Analyses

One of the theoretical issues that Meltzer and Smith (2011) discuss, is the perspective of the CEA, which is decisive for the design of the analysis and the cause of many controversies in the field. The perspective essentially refers to whose decision the CEA aims to inform. This is the source of the large variances observable in the practice of CEAs, because each decision maker has different needs. These differences will continue to exist but nevertheless there are some helpful guidelines regarding the perspective in the codification of CEA practices. The key insight is that the adopted perspective should exclusively depend on the decision-making context for which the CEA is designed. Once the perspective is determined, it should be decisive consistently throughout the design of the CEA (Edlin et al., 2015). Meltzer and Smith (2011) give several examples of possible perspectives, such as an analysis conducted from the perspective of a health care insurer. From this private perspective only costs and benefits that are relevant to the insurer should be taken into account. Examples of public perspectives include collective perspectives from health care systems alone, or broader governmental perspectives (Meltzer & Smith, 2011). The most inclusive perspective is a full-societal perspective, that includes all costs and benefits as a consequence of the intervention (Gold, Siegel, Russell, & Weinstein, 1996). Medical interventions can have effects beyond the health care system, and beyond the public domain, such as the impact on productive employment or travel costs. Meltzer and Smith (2011) discuss the advantages and disadvantages of full-societal perspectives. Taking into account the costs and benefits for any affected actor leads to a more accurate depiction of reality and the analysis comes closer to assessing whether there is a Pareto improvement, the change for which at least one individual is better off

without deteriorations for others. This can be a desirable perspective for governmental decision makers. The downsides of such perspectives relate to information availability and the feasibility of including all costs and benefits. Also, CEA outcomes are net effects of interventions, and do not demonstrate the distribution of the effects over different actors. This can only be solved by conducting separate analyses for different affected groups, which further increases the demand for information. If a truly full-societal perspective is adopted, it is no longer a cost-effectiveness analysis but a more general cost-benefit analysis (Meltzer & Smith, 2011). All costs and benefits, both within and beyond the health care sector, have to be included. These benefits and opportunity costs consist of a variety of non-market goods. In order to add these up, monetisation can no longer be avoided. The practical and ethical difficulties that arise from this were the reason for a general preference for the CEA method (Meltzer & Smith, 2011).

Claxton et al. (2010) set out two alternative less-inclusive perspectives compared to the full-societal perspective. Costs and benefits for other public sectors than the health care sector can be internalised by extending the scope of the health care budget and treating them as if they fall under this budget, or by making transfers from the health care budget to other public budgets for opportunity costs and benefits. The objection to this approach is the risk to not appropriately assess the value of the intervention for society, because of limiting the scope of the analysis to the effects in public sectors (Meltzer & Smith, 2011). The second alternative is the traditional approach to not take into account any effects beyond the health care sector which entails the same objection, and a possibly larger risk to underestimate the effects of a medical intervention for society (Claxton, Walker, Palmer, & Sculpher, 2010). There are many theoretical reasons to prefer a full-societal perspective, such as the absence of biases and consistency (Jönsson, 2009). The feasibility in practice is limited because of the lack of information and data availability. Meltzer and Smith (2011) note that attempts to take a full or broader societal perspective are not often observed in the practice of health coverage decisions. The key developments regarding perspectives that include costs and benefits beyond the health care sector are the use of a wider range of modelling techniques and the sophistication of the valuation of outcome measures, such as subjective well-being (Marsh, Phillips, Fordham, Bertranou, & Hale, 2012).

However, both modelling techniques and valuation approaches require some sort of normative judgement. Marsh et al. (2012) therefore propose to intensify the collaboration between economists and public decision makers.

Whatever perspective is chosen, it should be consistent with the objective function and the budget constraint. The chosen perspective determines the definition of the benefits that are to be maximised and the inclusion of costs, in other words, which stakeholders are to be taken into account. The perspective is also decisive for the extent to which heterogeneity in the target population and uncertainty have to be taken into account in the CEA design (Meltzer & Smith, 2011).

Economic evaluation should optimise whatever the decision maker wants to optimise (Sugden & Williams, 1978). To conduct a CEA, this concept of benefits has to be operationalised. If benefits are welfare as a function of individual or collective utility, and this function adheres with the Pareto principle, and resource allocation changes due to exogenous shocks in health or income, it qualifies as a welfarist approach (Brouwer et al., 2008). The economic evaluation of health technologies usually focusses on the collective benefits of a targeted population. Alternatively, the benefits for one representative average individual can be maximised. In CEAs for health care decisions however, often an extra-welfarist approach is used with other outcomes than utility such as life years or the rate of survival. A CEA can maximise a disease-specific benefit for the medical intervention in question, for example the number of avoided asthma attacks. Although disease-specific benefits are often easy to measure and likely to be readily available, it withholds the decision maker to compare the outcomes with other cost-effectiveness analyses (Garber & Sculpher, 2011). Therefore, more general measures of health gains such as life expectancy are used in many CEAs. However, an increase in life expectancy as such does not say anything about the quality of life, while additional life years with a low quality of life are not necessarily desirable. Therefore, measures that combine quality and quantity of life such as quality-adjusted life years (QALYs) were developed. QALYs are the most commonly used measure of health benefits in CEAs because of their validity and feasibility (Garber & Sculpher, 2011). As discussed in the Handbook of Health Economics by Meltzer and Smith, and Garber and Sculpher (2011) each life year is adjusted for its quality, by multiplying the year with a quality weight. The quality

weight has a range of zero to one, where a quality weight equal to one stands for a state of perfect health. Quality and quantity of life are traded off on an equal basis, for example one year in a state of perfect health equals two years in a state of health with a quality weight of a half. Many methodological issues arise with the use of QALYs. The quality of life has to be assessed, for example through revealed preferences or with the use of questionnaires, while quality of life has many different dimensions and its assessment can differ with age. Therefore, standardised instruments such as the EQ-5D have been developed (Oppe, Devlin, & Szende, 2007). The EQ-5D is a questionnaire with five dimensions to obtain a generic measure of health. Still, other questions arise, such as whether health gains for elderly should be weighed equally to health gains for younger people. As with all methodological issues for the design of CEAs, the perspective of the analysis should be decisive for the choices made regarding the QALYs (Garber & Sculpher, 2011; Meltzer & Smith, 2011). In practice however, much will depend on the availability of data as well.

Once the benefits are defined and operationalised, the cost side has to be considered. Meltzer and Smith (2011) explain this with the economic theoretical foundation of true opportunity costs, the costs for the foregone consumption opportunities when allocating resources to the medical intervention in question. The inclusion of opportunity costs depends on the perspective in a similar manner as the definition of benefits. If a full-societal perspective is adopted, all the opportunity costs for society have to be included, such as medical costs, the costs of work absence and travel costs related to the medical intervention. The obvious difficulties are the decision on where to draw the line for the inclusion of costs and the obtainment of reliable data. If a narrower perspective is adopted, for example restricted to the public health care sector, the included costs are limited to medical costs. Under this perspective the costs to be included are defined more clearly and it is relatively more feasible to obtain reliable data, but still critical decisions have to be made (Meltzer & Smith, 2011).

One such decision is the time horizon of the analysis. The most accurate and inclusive analysis is the inclusion of the costs and benefits for the rest of the lifetime of the target population. In the case of a public health care perspective, this means that not only the direct medical costs related to an intervention but also the long-term medical costs have to be included. For example, in the comparison of implementing the use of

a new medical health technology to a baseline scenario where care takes place as usual, both scenarios should include all long-term medical costs such as medicinal use and hospitalisation later on in life. For an analysis with a time horizon beyond the moment of the intervention, additional costs due to incremental life years have to be included. In an early study by Garber and Phelps (1997) these future costs were deemed negligible but as Meltzer and Smith (2011) explain, ignoring these future costs will bias the analysis in favour of the intervention when using a long-term time horizon.

In a more than one-period analysis, future costs and benefits should be discounted to accurately depict their present value. However, if costs are expressed in monetary units, and dependent on the perspective come from a wide range of bearers, and benefits are expressed in non-monetary units, it is not obvious that a single discount rate can be used. As one of the methodological controversies in the field of CEA, there is a diversity of standpoints (Meltzer & Smith, 2011). Again Meltzer and Smith (2011) find the consensus among scholars in the importance of consistency with the perspective. The discount rates for costs and benefits should accurately depict the time preference and growth rate over time, if necessary separately.

The many decisions to be made on the design of the CEA probably form the most fundamental source of uncertainty in modelling the effects of medical interventions. In analyses with a longer time horizon, the more common type of uncertainty in economic evaluation comes into play as well, the uncertainty of the future values of the parameters. This type of uncertainty creates the risk of deciding to implement a medical intervention that turns out not to be cost effective. If the costs attached to making a wrong decision or the uncertainty around the value of the parameters is negligible, or the decision maker is not risk averse, it has been argued that the uncertainty should be ignored (Claxton, 1999). The CEA should use the best available data as the expected values of the parameters. Additional or more accurate data can be included when it becomes available, due to which the decision might have to be revised (Meltzer & Smith, 2011). When the risk is larger because there are high costs attached to making a wrong decision, there is much uncertainty on the future values of parameters, or the decision maker is risk averse, there are different approaches possible. The common approaches are to do a sensitivity analysis on the outcomes or

to use confidence intervals around the parameters and outcomes (Meltzer & Smith, 2011). Alternatively, the CEA can incorporate the costs of making wrong decisions and their reversal, although this is not a common approach in practice (Palmer & Smith, 2000). When the future costs and benefits are simulated by a mathematical model, the uncertainty can be addressed by doing probabilistic sensitivity analyses. In any approach, the difficulty of addressing uncertainty is the potential covariance between parameters. Meltzer and Smith (2011) mention a typical parameter in long-term CEAs for medical interventions whose future value is surrounded by uncertainty; the expected survival rate of the targeted population. The future survival rate can be affected by many external factors on the long term, but also by the medical intervention itself. If the targeted population is a narrowly defined group, the latter effect can be homogeneous. More often, there is heterogeneity in patients, because of which the medical intervention does not lead to the same benefits for each patient. This can have important implications for the outcomes of the analysis. Observable heterogeneity can be addressed by creating subgroups in the target population, and essentially conduct separate analyses for each subgroup. The decision to implement the medical intervention is then made separately, based on the cost effectiveness of each subgroup. If the heterogeneity is not observable and only known to patients, such discrimination is not possible. This should be taken into account in the underlying structure of the model, and the best approach is to use the expected benefits and costs, again dependent on the availability of data.

With these issues of CEA design in mind, the next subsection discusses decision making based on CEAs. To decide whether a medical intervention is implemented, a cost-effectiveness criterion is used. However, as Garber and Phelps (1997) found, the use of a uniform criterion for a population with much heterogeneity is unlikely to lead to Pareto-optimal resource allocation, because it fails to take into account the differences in effect of the intervention for the subgroups within the population. Therefore, the CEA-design decision on what the targeted population is for the medical intervention should consider the consequences of any heterogeneity in the population.

2.3.3 Decision Making in CEA

CEAs aim to inform decision makers on choices between different health interventions. The perspective is decisive for the components of the CEA to fulfil the

needs of the decision maker. Usually, the CEA and the decision are not conducted by the same individual or the same entity. The CEA is conducted by an economist, possibly with the help of other specialists in the field of medicine and epidemiology, and the results of the CEA are presented to the decision maker, for example a policy maker or a health insurer.

As explained in the previous subsection, Quality Adjusted Life Years (QALYs) are a commonly used outcome measure, because of the comparability between different analyses. It combines the quality of health and the quantity of life years. However, the results that are presented to the decision maker are not expressed in QALYs. The CEA compares one or more alternatives, such as a new health technology as alternative 1, to a reference point, for example the care as usual as alternative 0. The benefits are defined in QALYs. The analysis calculates the costs and the QALYs for each alternative applied to the target population, over the chosen time horizon. The comparison of the accumulated costs and benefits of each scenario result in the incremental costs and the incremental QALYs of the new health technology compared to the status quo. This result can be captured by a single expression, the incremental cost-effectiveness ratio (ICER), consisting of a numerator expressing the incremental costs and a denominator that expresses the incremental benefits, in this case the incremental QALYs, see Equation 1.

$$\frac{(C1-C0)}{(B1-B0)} \tag{1}$$

Garber and Sculpher (2011) explain decision making based on ICERs. If the objective is to allocate a fixed budget in an optimal manner, the alternatives should be ranked by ICER, and the alternatives with the lowest ICERs should be implemented until the budget is exhausted. If the alternatives are mutually exclusive, for example different diagnostic strategies for one condition, an acceptable threshold for the maximum costs per unit of health benefits has to be established. Alternatives that exceed this threshold should be excluded because they are not cost effective. This threshold is rather a political or normative than a scientific question and is often left open for the decision maker to determine. The analyst simply reports the cost-effectiveness ratio, which means that CEA actually pushes the monetisation of health benefits forward from the researcher to the decision maker (Garber & Sculpher, 2011). A possible

guideline for an acceptable threshold is the willingness to pay (WTP) for an incremental QALY. With this approach there is usually no hard line but a lower and upper boundary of the WTP per QALY, and these ranges differ per country (Braithwaite, Meltzer, King, Leslie, & Roberts, 2008). The decision problem that remains when multiple scenarios exceed the cost-effectiveness criterion can be solved by using game-theoretical principles. A scenario is strictly dominated when it has higher or equal costs than the alternative, but has lower incremental benefits. Strictly dominated options should be eliminated. The principle of extended dominance eliminates scenarios that are strictly dominated by a linear combination of two other scenarios. For the scenarios that are left it holds that higher costs translate into higher benefits (Drummond, O'Brien, Stoddart, Torrance, & Sculpher, 2005). The easiest way to do this is to depict the scenarios in a graph with the incremental benefits and the incremental costs on the axes (Meltzer & Smith, 2011).

3. Methodology

The cost-effectiveness analysis of this paper is operationalised through a Markov model. This is a mathematical framework used to model decisions regarding stochastic processes. It is commonly used for the economic evaluation of medical interventions. Its main advantage is that it evaluates both health and economic effects, and the covariance between them (Briggs & Sculpher, 1998). This chapter starts with a general explanation of the employed Markov model and its structure, followed by the assumptions of the model. The diagnostics strategies (section 3.2) and the health states and events (section 3.3) together form the process that is modelled to obtain the costs and benefits of each alternative.

3.1 Markov model

As explained earlier, there are several reasons to prefer modelling the effects of a medical intervention, as opposed to conducting a clinical trial. The Markov model is one possible framework to compare the health benefits and costs of two or more medical interventions. It is useful for modelling health events that occur repeatedly over time, and to incorporate the health effects on a longer term (Edlin et al., 2015, Chapter 5). That is why the Markov model is selected to compare the diagnostic strategies for atrial fibrillation (AF), a condition with consequences on the long term.

As became clear in chapter 2, the design of a CEA, and thus the design of a framework to operationalise the CEA like the Markov model, is determined by the perspective. The CEA in this paper adopts a narrow perspective, limited to the public health care sector, because of the difficulties explained above with broader perspective, such as limited data availability and the need to have a clear definition of what costs and benefits should be included. Comparability plays a role as well; the health care perspective is the most common way to assess the cost effectiveness of medical interventions.

With this perspective in mind, the targeted population is defined. The target population consists of men and women of age 65 and older that present themselves at the general practitioner (GP) with symptoms suggestive of atrial fibrillation. An age threshold is used because the risk of AF increases with age. It is set at the age of 65 based on other CEAs on AF diagnosis (Camm et al., 2010; Lord et al., 2013; Moran, Flattery, Teljeur, Ryan, & Smith, 2013). Additionally, European guidelines recommend anticoagulation treatment for individuals of 65 years or older that are diagnosed with AF, such that the potential diagnosis of people in the targeted population is clinically relevant (Camm et al., 2010). This population is followed for the rest of their lifetime, under the assumption that no one becomes older than 105 years. Separate discount rates are used for the costs and benefits. Costs are discounted at a rate of 1,5% and health benefits at a rate of 4% based on Dutch guidelines for pharmacoeconomic research (The Health Care Insurance Board (CvZ), 2006).

The Markov framework models the benefits and costs of alternatives, in this case different diagnostic strategies (section 3.2), in the following manner. The individuals of the population are in one of the health states of the model, such as ‘Healthy’ or ‘Detected AF patient’ (section 3.3). To each health state the accompanying costs and the consequences for the quality of life are assigned. The cycle time of the model is six months, which is the smallest clinically relevant amount of time and is based on other CEAs on AF (Lord et al., 2013). After one cycle, individuals can move to a different health state or remain in the same health state, based on transition probabilities. These probabilities, based on data from publications, express the chance that for example a healthy individual from the target population transfers from the health state ‘Healthy’ to the health state ‘Detected AF patient’.

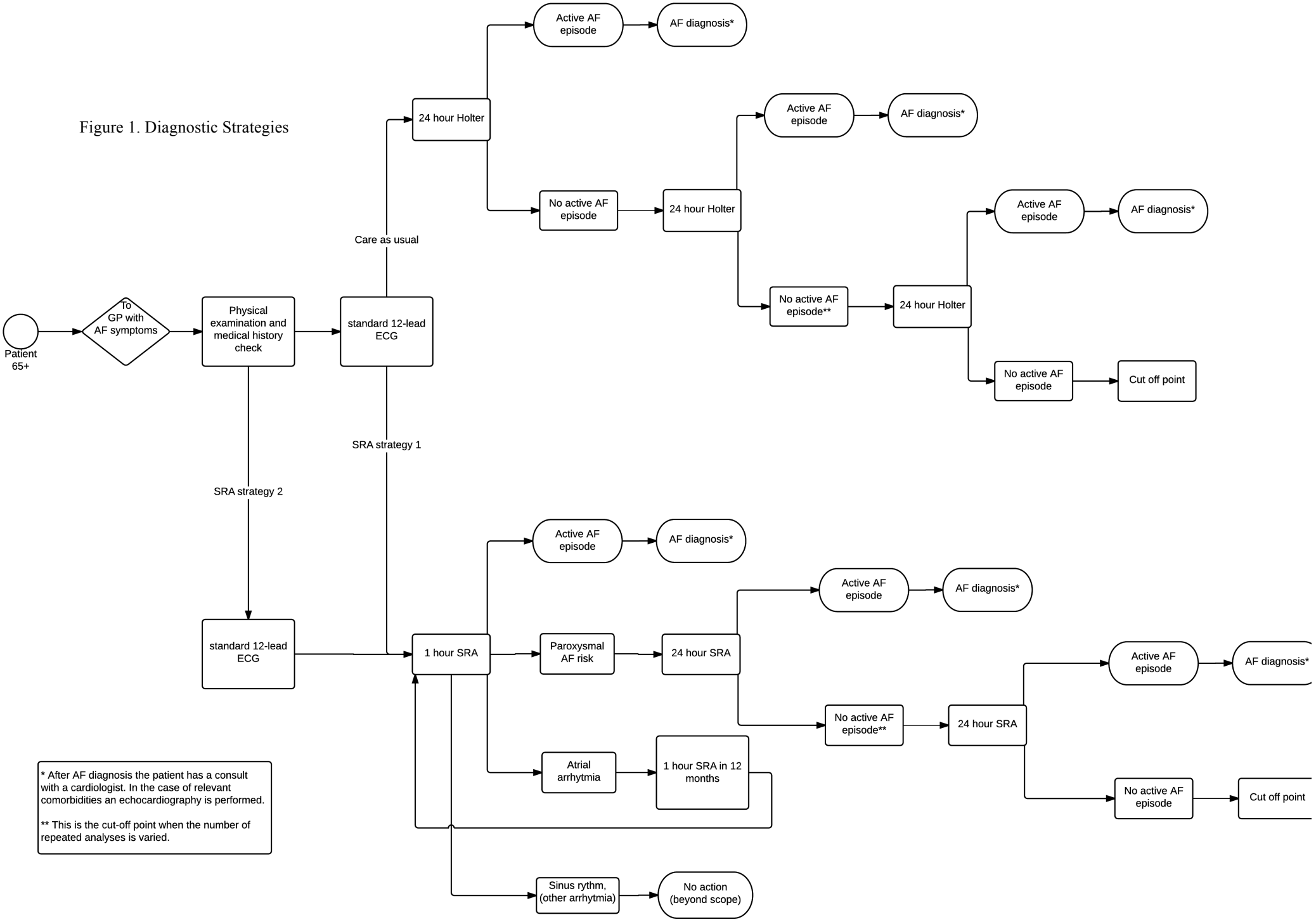
The Markov model is operationalised by obtaining data on all the necessary parameters. The data is entered into an Excel file, which simulates the cycles for each alternative, until there are no more individuals alive. For each alternative, the costs and benefits are accumulated. The costs and benefits for two alternatives are compared, such that the incremental costs, benefits and their ratio is obtained.

3.2 Diagnostic strategies: Care as usual and SRA

The target population is subject to three different diagnostic strategies, which are combinations of diagnostic tools. An overview of the diagnostic processes is depicted in Figure 1, and the sensitivities and specificities of the diagnostic strategies, and their references can be found in Appendix 1. For each diagnostic tool, testing positive means that evidence for AF is found. Individuals that test positive can include both true and false positives, where false positive means that a test incorrectly finds evidence for AF for individuals that do not suffer from AF. The sensitivity of a test refers to the ratio of true positive results to the sum of true positives and false negatives, whereas the specificity is the ratio of true negative results to the sum of true negatives and false positives.

The reference strategy, Usual Care, describes the current process of AF diagnosis in the Netherlands (The Dutch College of General Practitioners (NHG), 2013). Each individual, by definition of the target population, attends a general practitioner (GP) with symptoms suggestive of AF. The GP performs a physical examination (PE) and checks the medical history of the individual in the electronic medical record (EMR) of the patient. Subsequently, a standard 12-lead ECG is performed for the patients that test positive, both true and false, under the physical examination and medical history. If the PE and EMR check turn out negative, no further diagnostic tools are employed and both true and false negatives are excluded from the diagnostic process. The 12-lead ECG records the electrical activity of the heart over a short period of time, usually 10 seconds, by 12 electrodes attached to the body (NHG, 2013). Detection of an AF episode by the 12-lead ECG leads to the diagnosis of AF. If the 12-lead ECG does not detect an AF episode, a 24-hour Holter analysis is performed, which is an ECG of 24 hours that is analysed by a Holter analyst to detect active AF episodes (NHG, 2013). This baseline scenario of Usual Care is varied by repeating the 24-hour Holter analysis up to three times, if no AF diagnosis is established in the meantime.

Figure 1. Diagnostic Strategies



At any point, an AF diagnosis is followed by the referral to a cardiologist for treatment (Moran et al., 2013). The cut-off point of a maximum of three Holter analyses is based on the guideline model for atrial fibrillation developed by the English National Institute for Health and Care Excellence (NICE) (Lord et al., 2013).

The alternative strategy, SRA 1, starts similarly with checking the EMR and performing a PE. True and false negatives are excluded. True and false positives are followed up by a 12-lead ECG. A variation of this strategy is included in the model, strategy SRA 2, which does not exclude anyone after the PE and EMR check such that for every individual a 12-lead ECG is performed. This variation is included in the model because 6,3 per cent of the individuals test falsely negative based on the PE and the EMR (Hoefman et al., 2008). After the 12-lead ECG, SRA 1 and SRA 2 follow an identical process. The 12-lead ECG can detect AF, such that AF is diagnosed and the individual is not further tested. If the 12-lead ECG turns out negative, a one-hour Stroke Risk Analysis (SRA) is performed. SRA is a relatively new diagnostic tool for AF compared to the Holter analysis. It makes a recording of the electrical activity of the heart as well, to which an algorithm is applied. The SRA can detect AF patients without active AF episodes during the recording, because the algorithm recognises the specific signs prior to or subsequent to an AF episode (Schaefer et al., 2014). In the baseline scenarios of the diagnostic strategies SRA 1 and SRA 2, a single one-hour SRA test is performed. Similar to the Usual Care strategy, the baseline scenarios are varied by repeating the SRA test up to three times. However, the second and third SRA test are both 24-hour recordings. Again, patients that are diagnosed with AF at any point in the diagnostic process are referred to a cardiologist for treatment (Moran et al., 2013).

3.3 Health states and events

The Markov model contains five health states and different events, see Figure 2. At the beginning of the simulation, at time $t = 0$, each diagnostic strategy is applied to the targeted population. Now, for each different scenario, that is for each diagnostic strategy and their variations in terms of repetition of the main test, an initial distribution exists over the health states in which the individuals remain for at least 6 months, the cycle time of the model. After 6 months, the simulation runs again and individuals can move to different health states, and specified events can occur. The

probability with which an individual moves to a different health state, remains in its current health state or is subject to an event is the transition probability. For each health state, the transition probabilities express the chance that an individual will move to any of the other health states or is subject to an event. In Appendix 2 a summary of the transition probabilities and their references can be found.

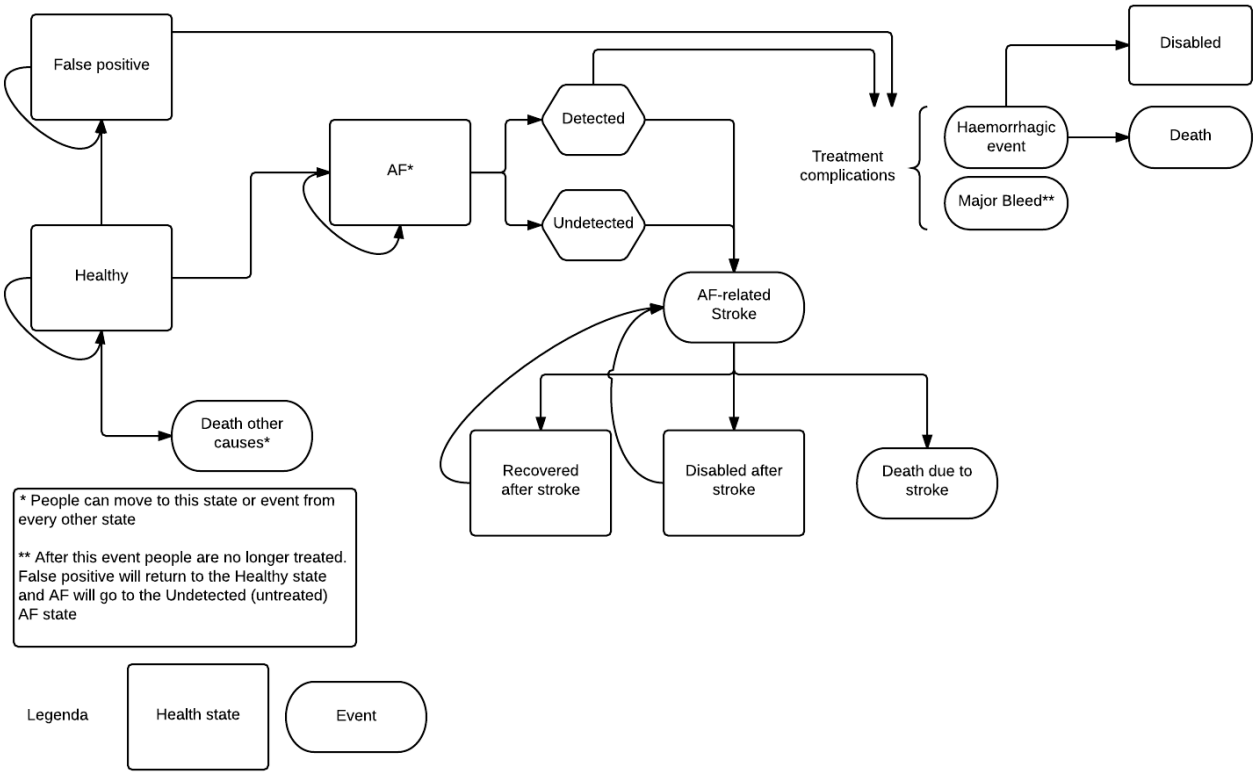


Figure 2. Health states of the Markov model

The following health states and events have been identified based on the characteristics of AF (Lord et al., 2013). The health state 'Healthy' consists of healthy individuals, which means that they do not suffer from AF and have not been diagnosed with it. The health state 'False Positive' also contains individuals that do not suffer from AF but they have been incorrectly diagnosed with AF. This health state is included because the anticoagulation treatment that follows diagnosis is subject to complications (Camm et al., 2010). AF patients that are detected also receive anticoagulation treatment and are subject to the same risk on treatment complications. Two possible treatment complications are included as events, with one-off costs and a negative effect on the quality of life after which the individual immediately continues to the next health state. After a major bleed, the

anticoagulation treatment is stopped and a one-off cost and negative effect on the quality of life is incurred. Falsely positive diagnosed individuals move to the health state 'Healthy' and detected AF patients move to the the health state 'Undetected AF Patients' because they no longer receive treatment. An haemorrhagic event is a more serious treatment complication due to anticoagulation therapy, after which a one-off cost is incurred. The event is either fatal, or the individual moves permanently to the health state 'Disabled'.

AF patients can suffer from AF-related strokes. Undetected AF patients do not receive treatment and are therefore subject to an increased risk on AF-related strokes compared to detected AF patients. AF-related strokes cause a one-off cost. If the stroke is not fatal, individuals immediately continue to the next health state 'Recovered after stroke' or 'Disabled after stroke', where they remain for at least two cycles after the stroke, with the appropriate medical costs and effects on quality of life attached to it. It is possible for an individual to suffer from multiple strokes, and after each stroke the chances of survival and recovery decrease.

Finally, at any point in time individuals in any health state can die because of other causes, which is incorporated as an event based on the general mortality in the Netherlands for the target population. The simulation is run, until the mortality rate equals one, with a maximum age of 105 years. For each scenario the costs and benefits are accumulated, such that the scenarios can be compared to obtain the incremental cost-effectiveness ratios, the subject of chapter 4. Appendix 2 contains an overview of all the parameters used for the transition probabilities, the quality of life, the costs attached to the health states and events and the background mortality risk.

4. Analyses and Results

For each scenario of each diagnostic strategy the costs and quality-adjusted life years are accumulated and divided by the population size. This is done separately for men and women because of the different parameters in for example background mortality (see Appendix 2). The first analysis compares within each diagnostic strategy the different scenarios. Scenarios are the variations of a diagnostic strategy in the frequency of the main test. For example, for the diagnostic strategy Usual Care the baseline scenario with one Holter test is compared to the Usual Care scenario with

two repetitions of the Holter test. To calculate the incremental cost-effectiveness ratio, first the costs of the scenario with 1 test (*C0*) are subtracted from the costs of the scenario with 2 tests (*C1*), resulting in the numerator of the ratio. Then, the quality-adjusted life years of the scenario with 1 test (*B0*) are subtracted from the quality-adjusted life years of the scenario with 1 test (*B0*) to calculate the denominator of the ratio, see Equation 1.

$$\frac{(C1-C0)}{(B1-B0)} \quad (1)$$

As Table 1 shows, repeating the main test does not lead to positive incremental cost-effectiveness ratios. The discounted ICERs, and the undiscounted ICERs alike, are negative because repeating the main test increases costs but decreases QALYs (see Appendix 3 for the undiscounted results). The second row of Table 1 takes the scenario with 2 tests as the reference point. From the negative ICERs it follows that comparing 1-test scenarios to 3-tests scenario will not improve the cost effectiveness either. For example, the first ICER in Table 1 of -€ 18.525 is the ICER of the comparison of 1 test to 2 tests within the Usual Care strategy for men. The increase in the frequency of the test led to a discounted increase in costs of € 6.870. However, the quality-adjusted life years for a man in the target population decreased on average by 0,371. Therefore, the resulting ratio is negative.

	Usual Care		**SRA 1**		**SRA 2**	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
1 to 2 tests	-€ 18.525	-€ 19.142	-€ 19.144	-€ 19.680	-€ 19.338	-€ 19.929
2 to 3 tests	-€ 18.570	-€ 19.196	-€ 19.216	-€ 19.767	-€ 19.428	-€ 20.005

Table 1. Discounted ICERs comparison frequency main test per diagnostic strategy

This is evident from Figure 3, in which the incremental costs and QALYs are plotted on which the ICERs in Table 1 are based. The increases in frequency of the main test for each diagnostic strategy increase costs and are accompanied by a decrease in QALYs. Testing more frequently in any of the strategies increases the number of diagnosed AF patients. The AF patients receive treatment, such that their increased risk of AF-related stroke is reduced, which increases their QALYs. These positive health benefits due to avoided strokes are outweighed by negative health effects, caused by treatment complications. Any positive health benefits from AF diagnosis

and the avoidance of stroke are dominated by the negative effects of treatment complications.

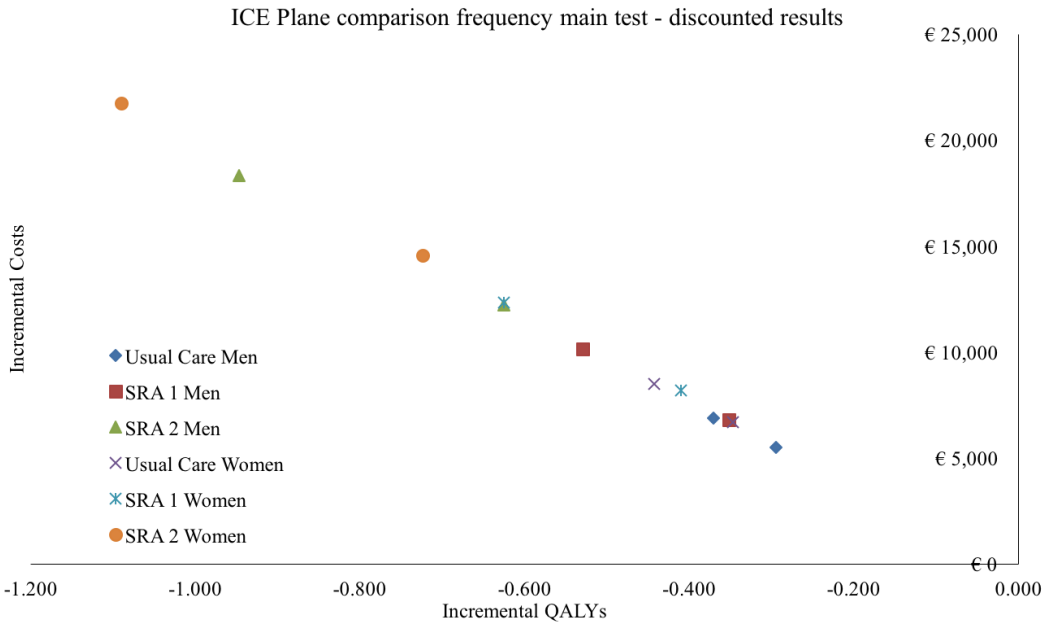


Figure 3. Discounted ICER comparison frequency main test

These results indicate that the SRA strategies are not going to be cost effective compared to Usual Care. This is confirmed by the discounted ICERs in Table 2 (see Appendix 3 for the undiscounted results). Similar to the comparison of the frequency of the main tests, comparing the strategies to each other for each frequency separately leads to negative ICERs. The use of SRA, regardless of the manner in which the preceding tests are conducted which is the difference between SRA 1 and SRA 2, is not cost effective compared to Usual Care.

Several characteristics of the model contribute to this result. The sensitivities of SRA 1 and SRA 2 are higher than the sensitivity of Usual Care (see Appendix 1). With a higher sensitivity, more true positive AF patients are found. However, the increase in sensitivity comes at the cost of a trade-off with specificity, the ratio of true negatives to all non-AF patients (the sum of true negatives and false positives). In other words, not only more true positive but also more false positive AF patients are found. The specificity of SRA 1 and SRA 2 is lower compared to Usual Care, such that the SRA strategies detect more false positives compared to Usual Care. This means that more individuals that are not AF patients are treated with anticoagulation therapy and are at risk for treatment complications, which are costly both in terms of health as in health

economic effects. Moreover, these falsely positive diagnosed individuals are not at an increased risk of stroke, such that they do not derive any health benefit from anticoagulation treatment. Only true positive individuals derive health benefits from treatment, for whom the reduction in the risk of AF-related stroke might outweigh the risk of treatment complications. The higher sensitivity of the SRA strategies also increases other costs. The increase in true and false positive cases under the SRA strategies also increases total treatment costs and the cardiologist costs, because all positive cases are referred to a cardiologist.

	1 test		**2 tests**		**3 tests**	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*
Usual Care – SRA 1	-€ 21.445	-€ 22.440	-€ 21.005	-€ 21.734	-€ 21.301	-€ 21.975
Usual Care– SRA 2	-€ 19.654	-€ 20.081	-€ 19.727	-€ 20.213	-€ 19.839	-€ 20.327
SRA 1 – SRA 2	-€ 19.360	-€ 19.654	-€ 19.430	-€ 19.840	-€ 19.506	-€ 19.936

Table 2. Discounted ICERs comparison diagnostic strategies per main test frequency

The ICERs from Table 1 and 2 show that in all comparisons there is a larger increase in costs per QALY for women than for men. The explanatory factors for this result are the following. Women have a higher life expectancy, such that an increase in the diagnosis of AF patients among women increases long term costs by more, compared to incremental long term costs for an equal increase in male AF patients. Also, women have a higher risk of stroke, although the prevalence of AF is lower among women compared to men (see Appendix 2).

In the interpretation of the results, it is important to note that the ICERs are all negative, because of the manner in which the strategies and their scenarios are compared. For example, the first row of Table 2 takes Usual Care as the reference strategy. The negative results imply that for each frequency of the main test, the Usual Care diagnostic strategy is the most cost-effective option compared to SRA 1 and SRA 2. Each row of Table 1 and 2 can be interpreted in the same way, the reference strategy is the relatively most cost-effective option. The third row of Table 2 takes SRA 1 as the reference point, but the choice to perform a 12-lead ECG on all individuals regardless of the results of their physical examination and electronic medical record check, as is done under SRA 2, does not improve the cost effectiveness compared to excluding the negative cases after the PE and EMR check,

the diagnostic process of SRA 1. This result is intuitive because of the relatively high rate of true negative cases (40,3%) compared to the false negative cases (6,3%) of the PE and EMR check (see Appendix 1). Both the true and the false negative cases are tested further in the SRA 2 strategy, while this only makes sense for the 6,3 per cent of false negative cases.

Underlying the result that cost effectiveness is not improved by an increase in sensitivity are the relatively good stroke outcomes in developed countries such as the Netherlands. According to the WHO, strokes have a seven time larger negative impact on QALYs in developing countries compared to developed countries (Mathers, Lopez, & Murray, 2006). Diagnostic strategies with higher sensitivities detect more AF patients, and their risk of stroke is mitigated by treatment accompanied by the risk of treatment complications. The result that the risk of treatment complications outweigh the benefits of increased AF diagnoses and stroke avoidance was also found in a CEA conducted by the English National Health Service (NHS) in 2014 (Solutions for Public Health (SPH) National Health Service (NHS), 2014). This study used a similar target population of 65 years and older. Different diagnostic tools were used, and it analysed the cost effectiveness of screening instead of individuals with AF-suggestive symptoms that attend a general practitioner as in the present CEA. Despite these differences, the similarities in the results are striking. Treatment complications of AF are detrimental for incremental health benefits gained with improved diagnostic strategies, at least for developed countries.

5. Conclusions and Discussion

Cost-effectiveness analyses of medical interventions aim to replicate consumption decisions to optimally allocate resources, because the health care market is characterised by many imperfections. These CEAs are often conducted with the help of simulation models because clinical trials are costly. This paper compared the cost effectiveness of the current common diagnostic strategy for atrial fibrillation to strategies that use a new health technology, with such a simulation model from the perspective of the health care sector. This narrow perspective was adopted, despite the fact that AF and strokes clearly have effects beyond the health care sector, for reasons of data availability and comparability to other CEAs of medical interventions. As recommended by the literature on the CEA method, the adopted perspective was

decisive for the design of the CEA, which included the direct and long term medical costs and health benefits in terms of quality-adjusted life years for a targeted population. The diagnostic strategies were applied to a group of men and women aged 65 and older that attended their general practitioner with symptoms suggestive of AF, after which a Markov model simulated the costs and health effects in terms of quality-adjusted life years for the rest of the population lifetime. The results of the different strategies and variations thereof were compared to each other, to answer the research question: 'What is the most cost-effective strategy in terms of costs per quality-adjusted life year to diagnose AF?'. The comparative analyses led to the conclusion that even though the diagnostic strategies that use the new diagnostic tool SRA are able to diagnose more AF patients, these strategies are not cost effective compared to the current common diagnostic strategy. On the contrary, the use of the new diagnostic tool does not lead to an increase in QALYs because the health benefits of avoided strokes in newly diagnosed AF patients are outweighed by the risk of treatment complications. Therefore, Usual Care is the most cost-effective diagnostic strategy, with a single Holter analysis. The underlying explanation for this result is the inevitable trade-off between the sensitivity and specificity of diagnostic tools. The SRA strategies are able to diagnose more AF patients and reduce their increase stroke risk with treatment, but at the same time lead to more falsely positive diagnoses. The incorrectly diagnosed individuals receive treatment and are at risk for treatment complications, while they do not derive any benefit from treatment. The simulation model demonstrated that these negative health effects dominate the positive health effects of mitigated stroke risks of AF patients.

Although these results are in line with another recent cost-effectiveness analysis of diagnosing AF in elderly people, there are several limitations to the research of this paper. The parameters for the construction of the model were obtained from many different publications and sources. Limited data availability formed an impediment and led to the adjustment of the structure of the model in certain instances. For example, the risk of treatment complications differs for individuals, dependent on factors such as comorbidities. This was simplified to an average risk in the model. The data on quality of life for the health states and events was especially difficult to obtain, while for quality of life in particular the obtainment from different sources is

likely to lead to inconsistencies. The parameters are obtained from different studies, based on different study populations, and sometimes also through different questionnaires. Another limitation is the assumption that individuals in the target population attend the general practitioner only once, at time *t=0*. In practice, individuals that test negative can return to the general practitioner later on in life to be diagnosed. Also, different diagnostic tools exist outside the incorporated diagnostic strategies, and as explained in the literature review, the physician's choice on the supply side is affected by many different incentives.

In this CEA the uncertainty of the parameters is not addressed. In a Markov model, this can for example be done through probabilistic sensitivity analyses. A so-called Monte Carlo simulation runs the model numerous times, and based on the standard deviations of each parameter, the probabilistic values are returned. However, as explained in the literature review, the most fundamental source of uncertainty in simulations models for CEAs is probably the risk of failing to accurately model the reality of the diagnostic processes, thus flaws in the design of the model itself. Moreover, when interpreting the results, the decision maker should keep in mind that these are based on a partial equilibrium approach, and the effects of the diagnostic strategies go beyond the health care sector and even beyond the public domain. Only a full-societal perspective, in a cost-benefit analysis, can come close to a general equilibrium model to assess Pareto improvements. In this particular model, especially costs due to work absence of individuals are likely to be significant, however it is not consistent with the health care sector perspective to include these costs.

For future research on the cost effectiveness of diagnostic strategies of AF it would be interesting to analyse the results from a broader perspective. Difficulties with limited data availability could be overcome by conducting a short-term clinical trial during which all costs are measured, and then extrapolated to a longer time horizon. In general, the field of CEAs of medical interventions would greatly benefit from closer cooperation between economists and other involved researchers such that data availability on costs and benefits is improved and modelling techniques are further developed.

Appendices

Appendix 1 Parameters of the Diagnostic Strategies

1.1 Sensitivities and Specificities

0. Usual Care: EMR/PE + 12-lead ECG + Holter (max. 3)	EMR/PE	12-lead ECG	Holter	**Total**	**Total (2x Holter)**	**Total (3x Holter)**
True Positive	0,126	0,054	0,184	**0,115**	**0,184**	**0,241**
False Negative	0,063	0,014	0,284	**0,195**	**0,171**	**0,151**
Correctly further tested	0,126	0,014	0,284			
False positive	0,409	0,078	0,000	**0,042**	**0,042**	**0,042**
True Negative	0,402	0,854	0,532	**0,648**	**0,603**	**0,566**
Incorrectly further tested	0,409	0,854	0,532			
Further tested total	***0,535***	***0,867***	***0,816***			
Sensitivity				0,370	0,519	0,615
Specificity				0,939	0,935	0,931

1. SRA 1: EMR/PE + 12-lead ECG + SRA1h + SRA24h (max.2)	EMR/PE	12-lead ECG	SRA 1hr	**Total**	SRA 24h	**Total (SRA 24)**	**Total (2x SRA 24)**
True Positive	0,126	0,054	0,270	**0,155**	0,279	**0,249**	**0,313**
False Negative	0,063	0,014	0,189	**0,151**	0,184	**0,125**	**0,106**
Correctly further tested	0,126	0,014	0,189		0,184		
False positive	0,409	0,078	0,005	**0,044**	0,032	**0,055**	**0,063**
True Negative	0,402	0,854	0,535	**0,650**	0,505	**0,571**	**0,518**
Incorrectly further tested	0,409	0,854	0,535		0,505		
Further tested total	***0,535***	***0,867***	***0,724***		***0,688***		
Sensitivity				0,506		0,666	0,748
Specificity				0,936		0,912	0,892

2. SRA 2: EMR/PE/12-lead ECG + SRA 1h + SRA 24h (max. 2)	EMR/PE	12-lead ECG	SRA 1hr	**Total**	SRA 24h	**Total (SRA 24)**	**Total (2x SRA 24)**
True Positive	0,000	0,054	0,270	**0,289**	0,279	**0,464**	**0,585**
False Negative	0,000	0,014	0,189	**0,164**	0,184	**0,116**	**0,080**
Correctly further tested	1,000	0,014	0,189		0,184		
False positive	0,000	0,078	0,005	**0,083**	0,032	**0,103**	**0,117**
True Negative	0,000	0,854	0,535	**0,464**	0,505	**0,317**	**0,218**
Incorrectly further tested	0,000	0,854	0,535		0,505		
Further tested total	***1,000***	***0,867***	***0,724***		***0,688***		
Sensitivity				0,638		0,801	0,880
Specificity				0,848		0,754	0,651

Separate diagnostic tests

5. Holter 24 hour	pxAF	AF
(Schaefer et al., 2014)		
True Positive	0,111	0,184
False Negative	0,298	0,284
False Positive	0,000	0,000
True Negative	0,591	0,532
Percentage further tested	0,889	0,816

4. SRA 24 hour	
(Schaefer et al., 2014)	
True Positive	0,279
False Negative	0,184
False Positive	0,032
True Negative	0,505
Percentage further tested	0,688

3. SRA 1 hour	pxAF	AF
(Schaefer et al., 2014)		
True Positive	0,218	0,270
False Negative	0,194	0,189
False Positive	0,006	0,005
True Negative	0,582	0,535
Percentage further tested	0,776	0,724

2. ECG 12-lead	
(Hobbs et al., 2005)	
True Positive	0,054
False Negative	0,014
False Positive	0,078
True Negative	0,854
Percentage further tested	0,867

1. EMR & PE	
(Hoefman et al., 2008)	
True Positive	0,126
False Negative	0,063
Correctly further tested	0,126
False Positive	0,409
True Negative	0,402
Incorrectly further tested	0,409
Percentage further tested	0,535

1.2 Diagnostic Costs

Test name	Value	Reference
GP consult	€ 9,04	NZA, 2015
ECG 12-lead	€ 43,99	NZA, 2015
Holter 24 hour	€ 161,76	NZA, 2015
SRA 1 hour	€ 20,00	PMC, 2015
SRA 24 hour	€ 20,00	PMC, 2015
Cardiologist consult	€ 205,00	Open DIS data 2014

Appendix 2 Parameters of the Health States and Events

2.1 Transition probabilities

AF Prevalence and Incidence (Heeringa et al., 2006)

Prevalence	
Male	
Age	
65-69	0,05
70-74	0,07
75-79	0,13
80-84	0,15
≥85	0,18
All ages	0,09

Female

Age	**Age index**
65-69	0,03
70-74	0,05
75-79	0,06
80-84	0,13
≥85	0,17
All ages	0,08

Incidence		
Male		
Age	**%/person yr**	**%/6 months**
65-69	0,01	0,00
70-74	0,01	0,01
75-79	0,02	0,01
80-84	0,03	0,01
≥85	0,03	0,01
All ages	0,01	0,01

Female

Age	**%/person yr**	**%/6 months**
65-69	0,00	0,00
70-74	0,01	0,01
75-79	0,01	0,01
80-84	0,02	0,01
≥85	0,02	0,01
All ages	0,01	0,01

Risk of stroke for AF patients (Lip, Frison, Halperin, & Lane, 2010)

Stroke risk in AF patients

		Stroke rate (%/year)		*Stroke rate %/6 months*	
CHA2DS2-VASc	**Patients (n=7329)**	**Warfarin therapy**	**Adjusted for Warfarin***	**Warfarin therapy**	**Adjusted for Warfarin***
0	1	0,00%	0,0%	0,00%	0,0%
1	422	0,46%	1,3%	0,23%	0,7%
2	1230	0,78%	2,2%	0,39%	1,1%
3	1730	1,16%	3,2%	0,58%	1,6%
4	1718	1,43%	4,0%	0,72%	2,0%
5	1159	2,42%	6,7%	1,22%	3,4%
6	679	3,54%	9,8%	1,79%	5,0%
7	294	3,44%	9,6%	1,74%	4,9%
8	82	2,41%	6,7%	1,21%	3,4%
9	14	5,47%	15,2%	2,77%	7,9%

Average CHA2DS2-VASc score AF patients

Untreated		*Male*				*Female*			
Age	**Age index**	**≥**	**Mean score**	**Average %/year**	**%/6 months**	**+1 ≥**	**Mean score**	**Average %/year**	**%/6 months**
65-69 +1	**65**	2	3,94	2,436%	1,225%	3	4,36	2,72%	1,371%
70-74 +1	**70**	2	3,94	2,436%	1,225%	3	4,36	2,72%	1,371%
75-79 +2	**75**	3	4,36	2,724%	1,371%	4	4,96	3,21%	1,619%
80-84 +2	**80**	3	4,36	2,724%	1,371%	4	4,96	3,21%	1,619%
≥85 +2	**85**	3	4,36	2,724%	1,371%	4	4,96	3,21%	1,619%

Average CHA2DS2-VASc score AF patients

Treated		*Male*				*Female*			
Age	**Age index**	**≥**	**Mean score**	**Average %/year**	**%/6 months**	**+1 ≥**	**Mean score**	**Average %/year**	**%/6 months**
65-69 +1	**65**	2	3,94	0,868%	0,435%	3	4,36	0,97%	0,487%
70-74 +1	**70**	2	3,94	0,868%	0,435%	3	4,36	0,97%	0,487%
75-79 +2	**75**	3	4,36	0,971%	0,487%	4	4,96	1,14%	0,572%
80-84 +2	**80**	3	4,36	0,971%	0,487%	4	4,96	1,14%	0,572%
≥85 +2	**85**	3	4,36	0,971%	0,487%	4	4,96	1,14%	0,572%

The CHA2DS2-VASc score is a clinical prediction rule for the risk of stroke of AF patients, based on different risk factors (Gage et al., 2004). The AF patients in the target population are distributed over the different scores. The average stroke rates in AF patients are calculated by taking the weighted average of strokes for all possible CHA2DS2-VASc scores of that age and sex group. The stroke rates are converted from rates per year to rates per 6 months and adjusted for treatment or no treatment (Lip et al., 2010).

Prevalence of stroke in 2011 RIVM (per 1000)			
Age	**Age index**	*Male*	*Female*
65-69	**65**	34,59	23,68
70-74	**70**	51,00	33,01
75-79	**75**	67,32	43,52
80-84	**80**	78,09	53,90
≥85	**85**	79,00	61,85

Stroke survivors			
Age	**Age index**	*Recover*	*Disabled*
65-69	**65**	34,59	23,68
70-74	**70**	51,00	33,01
75-79	**75**	67,32	43,52
80-84	**80**	78,09	53,90
≥85	**85**	79,00	61,85

Treatment complications Warfarin therapy			
	Event	Risk %/year	Risk %/6 months
Compl1	Haemorrhage	1,900%	0,955%
Compl2	Other bleeds	1,800%	0,904%
Overall		1,850%	0,929%

Stroke outcomes and recurrence	
(Appelros, Nydevik, & Viitanen, 2003)	
Stroke recurrence 1-yr probability	0,09

(Hylek et al., 2003)	
Ratio stroke outcomes on Warfarin	
Fatal	0,05
Disability	0,46
Recovered	0,49
30-day mortality	0,13

Ratio stroke outcomes no treatment	
Fatal	0,14
Disability	0,45
Recovered	0,41
30-day mortality	0,22

2.2 Quality of life

	EQ5D	*Reference*
Healthy	0,80	(Aronsson et al., 2015; Browne et al., 1994)
AF detected	0,66	(Hobbs et al., 2005)
AF undetected	0,73	(Hobbs et al., 2005)
False positive AF	0,80	(Aronsson et al., 2015)
1st year Stroke survivor	0,5	(Van Exel, Scholte Op Reimer, & Koopmanschap, 2004)
Stroke Survivor	0,75	(Haacke et al., 2006)
Major Bleed	0,65	(Aronsson et al., 2015)
Disabled treatment complication	0,44	(Haacke et al., 2006)
Recovered after AF stroke	0,86	(Haacke et al., 2006)
Disabled after AF stroke	0,44	(Haacke et al., 2006)

2.3 Costs of health states and events

Health states, mean costs per 6 months (Ringborg et al., 2008; Schalij et al., 2012; Verhoef et al., 2012)						
	Diagnostics	**Interventions**	**Drug therapy**	**Consultations**	**Inpatient care**	**Total**
AF detected	€80	€399	€44	€29	€417	€968
AF undetected	-	€623	-		€652	€1.275
False positive AF	€80	€399	€44	€29		€551
Stroke survivor y1	-	-	-			€12.247
Stroke survivor	-	-	-			€2.777

Events, one-off costs (Buisman, Tan, Nederkoorn, Koudstaal, & Redekop, 2015; Roos et al., 2002; Schalekamp, n.d.; Verhoef et al., 2012)	
AF-related stroke (Acute)	€3.159
Hemorrhagic event (Acute + 1st year)	€49.131
Major Bleed	€12.093

2.4 Mortality

Background mortality risk per 6 months by age and sex

(Dutch Bureau of Statistics (CBS), 2014)

Average 2008-2012	**Men**	**Women**
65-75	0,007929455	0,004873415
70-75	0,013328428	0,007851721
75-80	0,024176106	0,014208929
80-85	0,043174506	0,027827046
85-90	0,075120326	0,054007067
90-95	0,130488668	0,101798306
95 or older	0,218986415	0,185319755
105	1	1

Mortality events

Due to AF-stroke	0,25	(Lin et al., 1996)
Hemorrhagic event	0,486	(Fang et al., 2007)
Other bleeds	0,051	(Fang et al., 2007)

Appendix 3 Results

ICER comparison frequency main test per diagnostic strategy

	Usual Care		**SRA 1**		**SRA 2**	
Undiscounted	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
1 to 2 tests	-€ 25.670	-€ 27.589	-€ 26.369	-€ 28.114	-€ 26.515	-€ 28.242
2 to 3 tests	-€ 25.700	-€ 27.612	-€ 26.449	-€ 28.199	-€ 26.612	-€ 28.325
Discounted	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
1 to 2 tests	-€ 18.525	-€ 19.142	-€ 19.144	-€ 19.680	-€ 19.338	-€ 19.929
2 to 3 tests	-€ 18.570	-€ 19.196	-€ 19.216	-€ 19.767	-€ 19.428	-€ 20.005

ICER comparison diagnostic strategies

	1 test		**2 tests**		**3 tests**	
Undiscounted	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
Usual Care – SRA 1	-€ 31.425	-€ 34.172	-€ 29.681	-€ 31.876	-€ 29.862	-€ 31.917
Usual Care– SRA 2	-€ 26.907	-€ 28.470	-€ 26.961	-€ 28.546	-€ 27.081	-€ 28.654
SRA 1 – SRA 2	-€ 26.154	-€ 27.418	-€ 26.325	-€ 27.719	-€ 26.439	-€ 27.869
Discounted	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
Usual Care – SRA 1	-€ 21.445	-€ 22.440	-€ 21.005	-€ 21.734	-€ 21.301	-€ 21.975
Usual Care– SRA 2	-€ 19.654	-€ 20.081	-€ 19.727	-€ 20.213	-€ 19.839	-€ 20.327
SRA 1 – SRA 2	-€ 19.360	-€ 19.654	-€ 19.430	-€ 19.840	-€ 19.506	-€ 19.936

Bibliography

Anthony, D. L., Herndon, M. B., Gallagher, P. M., Barnato, A. E., Bynum, J. P. W., Gottlieb, D. J., Fisher, E. S. & Skinner, J. S. (2009). How much do patients' preferences contribute to resource use? *Health Affairs*, *28*(3), 864–73.

Aronsson, M., Svennberg, E., Rosenqvist, M., Engdahl, J., Al-Khalili, F., Friberg, L., Frykman-Kull, V. & Levin, L. A. (2015). Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. *Europace*, 1023–1029.

Arrow, K. (1963). Uncertainty and the welfare economics of medical care. *The American Economic Review, 53*(5), 941-973.

Boadway, R. W., & Bruce, N. (1984). *Welfare economics*. B. Blackwell.

Braithwaite, R. S., Meltzer, D. O., King, J. T., Leslie, D., & Roberts, M. S. (2008). What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Medical Care*, *46*(4), 349–56.

Briggs, A., & Sculpher, M. (1998). An introduction to Markov modelling for economic evaluation. *PharmacoEconomics*, *13*(4), 397–409.

Brouwer, W. B. F., Culyer, A. J., van Exel, N. J. A., & Rutten, F. F. H. (2008). Welfarism vs. extra-welfarism. *Journal of Health Economics*, *27*(2), 325–338.

Browne, J. P., O'Boyle, C. a, McGee, H. M., Joyce, C. R., McDonald, N. J., O'Malley, K., & Hiltbrunner, B. (1994). Individual quality of life in the healthy elderly. *Quality of Life Research : An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *3*(4), 235–44.

Buisman, L. R., Tan, S. S., Nederkoorn, P. J., Koudstaal, P. J., & Redekop, W. K. (2015). Hospital costs of ischemic stroke and TIA in the Netherlands. *Neurology*, *84*(22), 2208–2215.

Camm, A. J., Kirchhof, P., Lip, G. Y. H., Schotten, U., Savelieva, I., Ernst, S., … Zupan, I. (2010). Guidelines for the management of atrial fibrillation. *European Heart Journal*, *31*(19), 2369–2429.

Campbell, E. G., Regan, S., Gruen, R. L., Ferris, T. G., Rao, S. R., Cleary, P. D., & Blumenthal, D. (2007). Professionalism in medicine: Results of a national survey of physicians. *Annals of Internal Medicine*, *147*(11), 795–802.

Chandra, A., Cutler, D., & Song, Z. (2011). Who Ordered That? The Economics of Treatment Choices in Medical Care. *Handbook of Health Economics,* 2, 397-432.

Claxton, K. (1999). The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *Journal of Health Economics*, *18*(3), 341–364.

Claxton, K., Walker, S., Palmer, S., & Sculpher, M. (2010). Appropriate Perspectives for Health Care Decisions. *York: Centre for Health Economics*, 1 – 86.

College voor Zorgverzekeringen (CvZ) - The Health Care Insurance Board. (2006). *Guidelines for pharmacoeconomic research. Updated version.* Amstelveen.

Drummond, M. F., Sculpher, M. J., Torrance, G. W., O'Brien, B. J., & Stoddart, G. L. (2005). *Methods for the Economic Evaluation of Health Care Programmes*. Oxford university press.

Dutch Bureau of Statistics (CBS) Background Mortality (2014.

Edlin, R., McCabe, C., Hulme, C., Hall, P., & Wright, J. (2015). *Cost Effectiveness Modelling for Health Technology Assessment.* Springer.

Fang, M. C., Go, A. S., Chang, Y., Hylek, E. M., Henault, L. E., Jensvold, N. G., & Singer, D. E. (2007). Death and Disability from Warfarin-Associated Intracranial and Extracranial Hemorrhages. *American Journal of Medicine*, *120*(8), 700–705.

Feldstein, P. (2011). *Health care economics*. Cengage Learning.

Fuster, V., Rydén, L. E., Cannom, D. S., Crijns, H. J., Curtis, A. B., Ellenbogen, K. a, Halperin, J.L., Kay, G.N., Le Huezey, J.Y., Lowe, J.E. & Olsson, S.B. (2011). 2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation. *Journal of the American College of Cardiology*, *57*(11), e101-e198.

Garber, A. M., & Phelps, C. (1997). Economic foundations of cost-effectiveness analysis. *Journal of Health Economics*, *16*(1), 1–31.

Garber, A. M., & Sculpher, M. J. (2011). Cost Effectiveness and Payment Policy. *Handbook of Health Economics,* 2, 471-497.

Garber, A. M., Weinstein, M. C., Torrance, G. W., & Kamlet, M. S. (1996). Theoretical foundations of cost-effectiveness analysis. *Cost-Effectiveness in Health and Medicine*, 25–53.

Gold, M. R., Siegel, J. E., Russell, L. B., & Weinstein, Mc. (1996). *Cost-effectiveness in health and medicine: report of the panel on cost-effectiveness in health and medicine*. Oxford: Oxford University Press.

Haacke, C., Althaus, A., Spottke, A., Siebert, U., Back, T., & Dodel, R. (2006). Long-term outcome after stroke: Evaluating health-related quality of life using utility measurements. *Stroke*, *37*(1), 193–198.

Healy, Paul & Pugatch, M. (2009). *Theory versus Practice Discussing the Governance of Health Technology Assessment Systems*. Stockholm Network.

Hobbs, F. D., Fitzmaurice, D. A., Mant, J., Murray, E., Jowett, S., Bryan, S., Raftery, J., Davies, M. & Lip, G. (2005). A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technology Assessment (Winchester, England)*, *9*(40).

Hoefman, E., Boer, K., Weert, H. Van, Boer, K., Reitsma, J., Koster, R., & Bindels, P. (2008). Huisartsen kunnen de kans op hartritme- stoornissen vaak niet goed inschatten, *51*(7), 320–325.

Jönsson, B. (2009). Editorial: Ten arguments for a societal perspective in the economic evaluation of medical innovations. *European Journal of Health Economics*, *10*(4), 357–359.

Lin, H. J., Wolf, P. a, Kelly-Hayes, M., Beiser, a S., Kase, C. S., Benjamin, E. J., & D'Agostino, R. B. (1996). Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*, *27*(10), 1760–4.

Lord, J., Willis, S., Eatock, J., Tappenden, P., Trapero-Bertran, M., Miners, A., Crossan, C., Westby, M., Anagnostnou, A. Taylor, S.J.E. & Mavranezouli, I. (2013). Economic modelling of diagnostic and treatment pathways in National Institute for Health and Care Excellence clinical guidelines: The Modelling Algorithm Pathways in Guidelines (MAPGuide) project. *Health Technology Assessment*, *17*(58), 1–150.

Lucas, F. L., Sirovich, B. E., Gallagher, P. M., Siewers, A. E., & Wennberg, D. E. (2010). Variation in cardiologists' propensity to test and treat is it associated with regional variation in utilization? *Circulation: Cardiovascular Quality and Outcomes*, *3*(3), 253–260.

Mackay, J., & Mensah, G. A. (2004). *The Atlas of Heart Disease and Stroke*. *Journal of Human Hypertension* (Vol. 19).

Marsh, K., Phillips, C. J., Fordham, R., Bertranou, E., & Hale, J. (2012). Estimating cost-effectiveness in public health: a summary of modelling and valuation methods. *Health Economics Review*, *2*(1), 17.

Mathers, C. D., Lopez, A. D., & Murray, C. J. L. (2006). The burden of disease and mortality by condition: data, methods, and results for 2001. *Global Burden of Disease and Risk Factors*, *45*, 88.

McClellan, M. (2011). Reforming payments to healthcare providers: the key to slowing healthcare cost growth while improving quality? *The Journal of Economic Perspectives*, *25*(2), 69–92.

McGuire, T. G. (2011). Demand for Health Insurance. *Handbook of Health Economics,* 2, 317-397.

Meltzer, D. O., & Smith, P. C. (2011). Theoretical Issues Relevant to the Economic Evaluation of Health Technologies. *Handbook of Health Economics*, 2, 433-469.

Moran, P. S., Flattery, M. J., Teljeur, C., Ryan, M., & Smith, S. M. (2013). Effectiveness of systematic screening for the detection of atrial fibrillation. *The Cochrane Database of Systematic Reviews*, *4*(4), CD009586.

Naccarelli, G. V, Varker, H., Lin, J., & Schulman, K. L. (2009). Increasing prevalence of atrial fibrillation and flutter in the United States. *The American Journal of Cardiology*, *104*(11), 1534–1539.

Oppe, M., Devlin, N. J., & Szende, A. (2007). *EQ-5D value sets: inventory, comparative review and user guide*. Springer.

Palmer, S., & Smith, P. (2000). Incorporating Option Values Into the Economic

Evaluation of Health Care Technologies. *Journal of Health Economics*, *19*(5), 755–766.

Pauly, M. V. (1974). Overinsurance and Public Provision of Insurance: The Roles of Moral Hazard and Adverse Selection. *The Quarterly Journal of Economics*, *88*(1), 44–62.

Ringborg, A., Nieuwlaat, R., Lindgren, P., Jönsson, B., Fidan, D., Maggioni, A. P., … Crijns, H. J. G. M. (2008). Costs of atrial fibrillation in five European countries: Results from the Euro Heart Survey on atrial fibrillation. *Europace*, *10*(4), 403–411.

Roos, Y. B. W. E. M., Dijkgraaf, M. G. W., Albrecht, K. W., Beenen, L. F. M., Groen, R. J. M., De Haan, R. J., & Vermeulen, M. (2002). Direct costs of modern treatment of aneurysmal subarachnoid hemorrhage in the first year after diagnosis. *Stroke*, *33*(6), 1595–1599.

Schaefer, J. R., Leussler, D., Rosin, L., Pittrow, D., & Hepp, T. (2014). Improved detection of paroxysmal atrial fibrillation utilizing a software-assisted electrocardiogram approach. *PLoS ONE*, *9*(2).

Schalekamp, T. (2007). *Effects of Cyp2C9 and Vkorc1 Polymorphisms and Drug Interactions on Coumarin Anticoagulation Control*. Utrecht University.

Schalij, M., Dubois, E., Boersma, E., Huisman, M., Middeldorp, S., van Dijk, E. & Dresde, D. (2012). Leidraad begeleide introductie nieuwe orale antistollingsmiddelen, 1–64.

Solutions for Public Health (SPH) National Health Service (NHS). (2014). *Screening for Atrial Fibrillation in People aged 65 and over A report for the National Screening Committee*.

Sommers, B. D., Beard, C. J., D'Amico, A. V, Kaplan, I., Richie, J. P., & Zeckhauser, R. J. (2008). Predictors of patient preferences and treatment choices for localized prostate cancer. *Cancer*, *113*(8), 2058–2067.

Sugden, R., & Williams, A. (1978). *The principles of practical cost-benefit analysis*. JSTOR.

The Dutch College of General Practitioners (NHG). (2013). NHG-Standaard Atriumfibrilleren (tweede partiële herziening). *Huisarts En Wetenschap*, *56*(8), 392–401.

Van Exel, N. J. A., Scholte Op Reimer, W. J. M., & Koopmanschap, M. A. (2004). Assessment of post-stroke quality of life in cost-effectiveness studies: The usefulness of the Barthel Index and the EuroQoL-5D. *Quality of Life Research*, *13*(2), 427–433.

Verhoef, T. I., Redekop, W. K., van Schie, R. M., Bayat, S., Daly, A. K., Geitona, M., Haschke-Becher, E., Hughes, D.A., Kamali, F., Levin, L.A. & Manolopoulos, V.G. (2012). Cost–effectiveness of pharmacogenetics in anticoagulation: international differences in healthcare systems and costs. *Pharmacogenomics*,

13(12), 1405–1417.

Zuckerman, S., Waidmann, T., Berenson, R., & Hadley, J. (2010). Clarifying sources of geographic differences in Medicare spending. *The New England Journal of Medicine*, *363*(1), 54–62.