Efficacy and cost-effectiveness of new oral anticoagulants compared to warfarin for the prevention of stroke in patients with atrial fibrillation

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Norwegian Knowledge Centre for the Health Services

Background: Warfarin has been used as the only oral anticoagulant for over 50 years in patients with atrial fibrillation. Recently new oral anticoagulants like dabigatran, rivaroxaban and apixaban have been developed for this indication. We compared these new oral anticoagulants with each other and with warfarin with respect to efficacy and cost-effectiveness for patients with atrial fibrillation and moderate or high risk of stroke. **Main findings:** • The new oral anticoagulants reported statistically significant reductions of intracranial bleeding compared to warfarin. For the outcomes all-cause mortality, ischemic stroke, gastrointestinal bleeding and myocardial infarction, results were inconclusive. The quality of evidence for the outcomes was generally regarded as low or very low. • Only one large randomised controlled trial presently exists for each of these three new oral anticoagulants, all compared to warfarin. This necessitated modelling through indirect comparisons. • Apixaban 5 mg x 2, dabigatran 150 mg x 2 and rivaroxaban 20 mg x 1 all seems to be cost-effective when each are compared to warfarin for patients with atrial fibrillation at medium and high risk of

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(continued from page one) stroke. • When all drugs are compared to each other, dabigatran 150 mg x 2 seems to be the most cost-effective in 28 of 30 individual risk groups and apixaban in the remaining three risk groups based on an assumed threshold cost-effectivness of NOK 588 000 per QALY. • The conclusions regarding efficacy and cost-effectiveness are highly uncertain. The conclusions may change if the assumptions in the model change. New research directly comparing the new oral anticoagulants with each other and with warfarin is likely to be useful and would reduce decision uncertainty.

Key messages

Warfarin has been used as the only oral anticoagulant for over 50 years in patients with atrial fibrillation. Recently new oral anticoagulants like dabigatran, rivaroxaban and apixaban have been developed for this indication. We compared these new oral anticoagulants with each other and with warfarin with respect to efficacy and cost-effectiveness for patients with atrial fibrillation and moderate or high risk of stroke.

- The new oral anticoagulants reported statistically significant reductions of intracranial bleeding compared to warfarin. For the outcomes all-cause mortality, ischemic stroke, gastrointestinal bleeding and myocardial infarction, results were inconclusive. The quality of evidence for the outcomes was generally regarded as low or very low.
- Only one large randomised controlled trial presently exists for each of these three new oral anticoagulants, all compared to warfarin. This necessitated modelling through indirect comparisons.
- Apixaban 5 mg x 2, dabigatran 150 mg x 2 and rivaroxaban 20 mg x 1 all seems to be cost-effective when each are compared to warfarin for patients with atrial fibrillation at medium and high risk of stroke.
- When all drugs are compared to each other, dabigatran 150 mg x 2 seems to be the most cost-effective in 28 of 30 individual risk groups and apixaban in the remaining three risk groups based on an assumed threshold cost-effectivness of NOK 588 000 per QALY.
- The conclusions regarding efficacy and cost-effectiveness are highly uncertain. The conclusions may change if the assumptions in the model change. New research directly comparing the new oral anticoagulants with each other and with warfarin is likely to be useful and would reduce decision uncertainty.

Executive summary

Background

Atrial fibrillation is an abnormality of the heart rhythm that leads to increased risk of stroke and other cardiovascular events, which in turn may lead to disability or premature death. The oral anticoagulant warfarin has been used for atrial fibrillation for more than five decades and is still widely used. Use of warfarin requires close monitoring and leads to numerous visits to the doctor. New oral anticoagulants dabigatran, rivaroxaban and apixaban probably require less intensive monitoring, but are more expensive drugs than warfarin. It is uncertain whether the new drugs are effective, safe and cost-effective in a Norwegian setting.

Objective

To calculate the cost-effectiveness of the new oral anticoagulants, apixaban, dabigatran and rivaroxaban, relative to each other and to warfarin for the prevention of stroke in patients with atrial fibrillation at different levels of risk.

Method

We performed a systematic literature search for systematic reviews and randomised controlled trials to inform us regarding efficacy and safety. Quality of efficacy documentation was assessed with GRADE.
We developed a decision analytic model for patients with atrial fibrillation. In the model, patients are assumed to be at elevated risk of stroke, myocardial infarction, bleeding and death. Epidemiological input data was gathered from mainly Scandinavian registries. Data on Quality of Life was based on EQ-5D data and costs were mainly based on Norwegian fees and schedules.

Results

We found one Canadian HTA report with a systematic review of clinical studies. The main efficacy data were based on three large randomized controlled trials comparing each of the new oral anticoagulants with warfarin. All three randomized controlled

trials reported statistically significant reductions of intracranial bleeding compared to warfarin. For the outcomes all-cause mortality, ischemic stroke, gastrointestinal bleeding and myocardial infarction, results were inconclusive. The quality of evidence for the outcomes was generally regarded as low or very low.

Model analyses indicated that the new drugs are likely to lead to some increase in remaining quality-adjusted life expectancy, but also increased costs. All three new anticoagulants are likely to be cost-effective compared to warfarin, but this conclusion is highly uncertain and depends heavily on model assumptions. For atrial fibrillation patients with moderate stroke risk, apixaban seems to be effective compared to the other anticoagulants, while the cost-effectiveness depends heavily on risk of bleeding. For high risk patients, dabigatran is likely to be cost-effective compared to the alternatives.

Discussion

Limited efficacy data is the major source of uncertainty in the analyses. Only one major trial compared each new drug to warfarin and no trials have compared any of the new oral anticoagulants with each other.
Currently, prices of the three new drugs are in a state of flux because of competition among the pharmaceutical companies. Because changes in drug prices affect cost-effectiveness estimates, the conclusions of this report may well need to be revised after the report is released.

Conclusion

Which of the oral anticoagulants is the most effective, the safest and the most cost-effective is highly uncertain.

Decision uncertainty could be reduced through large, independent, randomized controlled trials. The trials should ideally be done in different countries and directly compare the new drugs with each other and warfarin. This would also benefit patients.

Hovedfunn (norsk)

Warfarin har blitt brukt som eneste orale antikoagulant i over 50 år for pasienter med atrieflimmer. Nylig har nye orale antikoagulantia som dabigatran, rivaroksaban og apixaban blitt utviklet for denne indikasjonen. Vi sammenlignet disse nye orale antikoagulantene med hverandre og med warfarin med hensyn til effekt og kostnadseffektivitet for pasienter med atrieflimmer og moderat eller høy risiko for slag.

- De nye orale antikoagulantia rapporterte statistisk signifikant reduksjon av intrakraniell blødning sammenlignet med warfarin. For resultatene totaldødelighet, hjerneinfarkt, gastrointestinal blødning og hjerteinfarkt, var forskjellen mellom de nye antikoagulantia og warfarin ikke-signifikante. Kvaliteten på dokumentasjonen for utfallene var generelt ansett som lav eller svært lav.
- I dag finnes bare én stor randomisert kontrollert studie for hver av de tre nye orale antikoagulantia sammenlinget med warfarin. Indirekte sammenligninger er derfor nødvendig for å kunne si noe om de nye antikoagulantia sammenlignet med hverandre.
- Apixaban 5 mg x 2, dabigatran 150 mg x 2 og rivaroksban 20 mg x 1 synes alle å være kostnadseffektive når hver enkelt er sammenlignet med warfarin for pasienter med atrieflimmer med medium og høy risiko for hjerneslag.
- Når alle legemidler er sammenlignet i forhold til hverandre, synes dabigatran 150 mg x 2 å være den mest kostnadseffektive i 28 av 30 risikogrupper og apixaban i de resterende tre basert på en antatt referanseverdi for kostnadseffektivitet på 588 000 kroner per QALY.
- Konklusjonene om effekt og kostnadseffektivitet er svært usikre. Konklusjonene kan endres hvis forutsetningene i modellen endres. Ny forskning som direkte sammenligner nye orale antikoagulanter med hverandre og med warfarin vil sannsynligvis redusere usikkerheten rundt hvilke av disse medikamentene som er mest effektive og kostnadseffektive.

Sammendrag (norsk)

Bakgrunn

Atrieflimmer er en forstyrrelse av hjerterytmen som fører til økt risiko for hjerneslag og andre kardiovaskulære hendelser, som i sin tur kan føre til uførhet eller tidlig død. Den orale antikoagulanten warfarin har vært brukt for atrieflimmer i mer enn fem tiår og er fortsatt mye brukt. Bruk av warfarin krever tett oppfølging og fører til mange legebesøk. De nye orale antikoagulantene dabigatran, rivaroksaban og apixaban vil trolig kreve mindre intensiv overvåking, men er dyrere legemidler enn warfarin. Det er usikkert om de nye stoffene er effektive, sikre og kostnadseffektive i en norsk setting.

Problemstilling

Å beregne kostnadseffektiviteten av de nye orale antikoagulantene apixaban, dabigatran og rivaroksaban, i forhold til hverandre og i forhold til warfarin for forebygging av hjerneslag hos pasienter med atrieflimmer på ulike risikonivåer.

Metode

Vi søkte systematisk etter systematiske oversikter og randomiserte kontrollerte studier angående effekt og sikkerhet. Kvaliteten på effektdokumentasjonen ble vurdert med GRADE.

Vi utviklet en beslutningsmodell for pasienter med atrieflimmer. I modellen antas pasienter å ha forhøyet risiko for hjerneslag, AMI, blødning og død. Epidemiologiske data ble samlet inn hovedsakelig fra skandinaviske registre. Livskvalitetsdata var basert på EQ-5D og kostnader ble i hovedsak basert på norske takster.

Resultat

Vi fant en kanadisk HTA rapport med en systematisk oversikt over kliniske studier. Effektdata var i hovedsak basert på tre randomiserte kontrollerte studier som sammenlignet hver av de nye orale antikoagulantene med warfarin. Alle de tre randomi-

serte kontrollerte studiene rapporterte statistisk signifikant reduksjon av intrakra-
niell blødning sammenlignet med warfarin. For utfallene totaldødelighet, hjernein-
farkt, gastrointestinal blødning og hjerteinfarkt, var resultatene sprikende. Kvalite-
ten på dokumentasjonen for utfallene var generelt ansett som lav eller svært lav.

Modellanalysene tydet på at de nye legemidlene sannsynligvis vil føre til en viss øk-
ning i gjenværende kvalitetsjustert forventet levealder, men også økte kostnader.
Alle de tre nye antikoagulantene ser ut til å være kostnadseffektive sammenlignet
med warfarin, men denne konklusjonen er høyst usikker og avhenger sterkt av mo-
dellforutsetningene. For atrieflimmerpasienter med moderat risiko for slag, synes
apixaban å være effektiv i forhold til de andre antikoagulantene, mens kostnadsef-
fektiviteten avhenger av risiko for blødninger. For høyrisikopasienter, synes dabi-
gatran å være kostnadseffektivt sammenlignet med alternativene.

Diskusjon

Begrensede effektdata er den viktigste kilden til usikkerhet i analysene. Bare én stor
studie sammenlignet hvert nytt legemiddel med warfarin, og ingen studier har
sammenlignet noen av de nye orale antikoagulantene med hverandre.
Det er mulighet for at prisene på de tre nye medikamentene kan endres av konkur-
ranse mellom de farmasøytiske selskapene. Fordi endringer i medikamentprisene
påvirker kostnadseffektivitetsestimatene, kan det hende at konklusjonene i denne
rapporten må revideres etter at rapporten er utgitt.

Konklusjon

Hvilken av de orale antikoagulantene som er mest effektiv, sikrest og mest kost-
nadseffektiv er høyst usikkert.

Usikkerheten rundt beslutningen om bruk av oral antikoagulasjon kan reduseres
gjennom store, uavhengige, randomiserte kontrollerte studier. Forsøkene bør gjøres
i ulike land og direkte sammenligne de nye medikamenter med hverandre og warfa-
rin.

Nasjonalt kunnskapssenter for helsetjenesten fremskaffer og formidler kunnskap
om effekt av metoder, virkemidler og tiltak og om kvalitet innen alle deler av helse-
tjenesten. Målet er å bidra til gode beslutninger slik at brukerne får best mulig helse-
tjenester. Kunnskapssenteret er formelt et forvaltningsorgan under Helse-
direktoratet, men har ikke myndighetsfunksjoner og kan ikke instrueres i faglige
spørsmål.

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Glossary and abbreviations

ICER	**Incremental cost-effectiveness ratio**. The ratio of the difference in costs between two alternative health technologies to the difference in effectiveness between these two technologies. $$ICER = \frac{Cost_{intervention} - Cost_{comparator}}{Effect_{intervention} - Effect_{comparator}} = \frac{\Delta C}{\Delta E}$$
AF	**Atrial fibrillation** is an abnormality of the heart rhythm.
CEAC	**Cost-effectiveness acceptability curve.** Presents proportion of simulations from PSA that are cost-effective for different values of WTP
CEAF	**Cost-effectiveness acceptability frontier.** Version of CEAF where only values for the cost-effective option is displayed for varying WTP
CHADS2	**Risk score.** Different risk factors indicate increased risk of stroke among patients with atrial fibrillation. Total score ranges from 0 to 6, with the following scoring per risk factor: Congestive heart failure = 1, Hypertension = 1, Age>75 = 1, Diabetes mellitus = 1, Prior Stroke/TIA/thromboembolism = 2.
CHA$_2$DS$_2$-VASc	**Risk score.** Different risk factors indicate increased risk of stroke among patients with atrial fibrillation. Total score ranges from 0 to 9, with the following scoring per risk factor: Congestive heart failure = 1, Hypertension = 1, Age>75 = 2, Diabetes mellitus = 1, Prior Stroke/TIA/thromboembolism = 2, Vascular disease = 1, Age65-74 = 1, Sex (female) =1.
CI	**Confidence interval.** A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrow intervals, greater precision. Used in frequentist statistics. Analogous to CrI in Bayesian statistics.
CrI	**Credibility interval.** Used in Bayesian statistics. Analogous to CI in frequentist statistics.
CUA	**Cost-utility analysis.** An economic evaluation in which health consequences are measured in **QALY**s.
ESC	**European Society of Cardiology**
EVPI	**Expected value of perfect information.** EVPI represents the value of eliminating all uncertainty within a health economic model
EVPPI	**Expected value of perfect information on parameters.** EVPPI represents EVPI for single parameters og groups of parameters
GI bleeding	**Gastrointestinal bleeding**

HAS-BLED	**Risk score.** Different risk factors indicate increased risk of bleeding. Total score ranges from 0 to 7, with each the following risk factor scoring 1 point: Hypertension, Abnormal liver function, Stroke, Bleeding, Labile INR, Elderly (age >65) and drugs/alcohol**.**
HR	**Hazard ratio.** Ratio of hazard rates. Ratios above 1 indicate increased instantaneous rate of an event. Ratios below 1 indicate a decrease in event rates.
HTA	**Health technology assessment.** Multi-disciplinary overview of a policy question, contain a systematic review of the technology and an economic evaluation, and often also other implications like ethical, legal and organizational consequences
INHB	**Incremental net health benefit.** Difference in NHB between two interventions
NHB	**Net Health Benefit.** In a decision-making process, a positive NHB suggests that the intervention represents good value for money $$NHB \;=\; \Delta E - \frac{\Delta C}{\lambda}$$ Incremental net health benefit is the difference in net health benefit between two interventions
NMB	**Net Monetary Benefit.** In a decision-making process, a positive NMB suggests that the intervention represents good value for money. $$NMB = \lambda \cdot \Delta E - \Delta C$$
NOAC	New oral anticoagulant
NoMA	The Norwegian Medicines Agency
OR	**Odds ratio.** The ratio of the odds of an outcome in one treatment group divided by the odds of the same outcome in a different treatment group.
PSA	**Probabilistic sensitivity analysis.** An analysis of the uncertainty related to all parameters in a decision analytic model. Typically performed by Monte Carlo simulation, hence by drawing values from probability distributions for all parameters simultaneously
QALY	**Quality-adjusted life-year.** A measure of health outcomes that combines quantity and quality of life by assigning to each year of life a weight from 1 (perfect health) to 0 (state judged equivalent to death) dependent on the individual's health related quality of life during that year
RCT	**Randomised controlled trial.** An experiment in which investigators use randomisation to allocate participants into the groups that are being compared. Usually allocation is made at the level of individuals, but sometimes it is done at group level e.g. by schools or clinics. This design allows assessment of the relative effects of interventions.

RR	**Relative risk / risk ratio.** The relative risk is the absolute risk (AR) in the intervention group divided by the AR in the control group. It is to be distinguished from odds ratio (OR), which is the ratio of events over non-events in the intervention group over the ratio of events over non-events in the control group.
SR	**Systematic review.** A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Statistically significant	Means that the findings of a study are unlikely to be due to chance. Significance at the commonly cited 5% level (P < 0.05) means that the observed difference or greater difference would occur by chance in less than 5% similar cases. Where the word "significant" or "significance" is used without qualification in the text, it is being used in this statistical sense.
WTP (λ)	**Willingness to pay**. A pre-specified threshold of what society is willing to pay for a given health unit (e.g. QALY or life year). In Norway it has been suggested NOK 500 000 per QALY or life year in economic evaluations, although the existence of such a specific threshold is controversial. This number was proposed to be measured in NOK from 2005, which is approximately 588 000 in 2011 NOK.

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Preface

This project was commissioned by The Norwegian Medicines Agency (NoMA), which needed an independent assessment of whether any of the new oral anticoagulants (apixaban, dabigatran or rivaroxaban) are likely to be cost-effective in comparison with each other and with the existing alternative (warfarin) in preventing stroke in patients with atrial fibrillation.

The results of this HTA report may be used as scientific documentation in preparation of national stroke prevention guidelines, or to inform reimbursement decisions. Our independent model facilitates the comparison between several new anticoagulants, and can easily be updated with therapeutic options that become available in the future.

Tove Ringerike was lead reviewer for the clinical evaluation and Torbjørn Wisløff lead the health economic evaluation. Signe Agnes Flottorp, Vida Hamidi, Dan Atar and Bjarne Robberstad peer reviewed the report. We also thank Atle Fretheim and Brynjar Fure for comments.

The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preferences.

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Department director   *Research director*   *Project leader*

Objective

Main objective

To calculate the cost-effectiveness of the new oral anticoagulants (apixaban, dabigatran and rivaroxaban) relative to each other and to warfarin for prevention of stroke in patients with atrial fibrillation at different risk levels.

Other objectives

To compare the efficacy of new anticoagulants with warfarin in preventing morbidity and mortality for patients with atrial fibrillation.

To construct a model that calculates remaining quality adjusted life expectancy for patients with atrial fibrillation and disease-related costs along the clinical pathway.

Background

Introduction

Atrial fibrillation (AF) is an abnormality of the heart rhythm (1). The normal regular impulses are replaced by disorganized electric impulses in the atrial walls, resulting in irregular conduction of impulses to the main heart chambers (ventricles). The heart beats generated by the ventricles become irregular and in most cases the heart rate is rapid. AF may be accompanied by symptoms related to the rapid heart rate, such as palpitations, chest discomfort, shortness of breath, and chest pain. Sometimes AF is asymptomatic. AF may occur as reversible episodes of different duration and is then named paroxysmal AF. This is the usual initial appearance of the arrhythmia, but over time it often becomes chronic, a condition for which the term permanent AF is applied.

The main pathologic change seen in AF is a progressive fibrosis in the atrial walls, which means that an abnormal amount of fibrous tissue is formed. This may in turn be related to inflammatory processes. Because of the fibrosis, or due to hemodynamic alterations, the atria dilate and the blood flow pattern through the atria becomes changed. In this way the surface of the atrial walls, in particular in the left atrium, will be thrombogenic, that is to say it predisposes for unwanted blood clotting (2). The clotted blood, which is called a thrombus, appears initially in the atrium, but it may be released from the atrial wall and transported by the blood stream to the brain. Thus it may cause an ischemic stroke. Transportation to different parts of the body may also occur, resulting in what is called systemic embolism (peripheral embolism).

AF is a very prevalent disorder, and it increases markedly with age (1). At age 40-50 years less than 0.5% have AF whereas at age 80, 5-15% of the population have this arrhythmia. The lifetime risk of AF for men and women over age 40 is approximately 25 %, indicating that one in four elderly individuals will experience AF. It has been estimated that between 65 000 and 82 000 people in Norway have AF and that this number is expected to double within approximately 50 years (3).

Because AF patients are at risk of suffering a stroke or systemic embolism, prevention of such events is a main goal in the management of AF. Over the years anticoagulants – warfarin is the one used in most countries – have been shown to be most efficacious for stroke prevention. Compared with placebo warfarin reduces the stroke rate among AF patients by about 67% (4). Inhibitors of blood platelets, aspirin and clopidogrel, provide some protection but are far less beneficial than warfarin (5). Until recently warfarin, which is a vitamin K antagonist, has been without competition from other anticoagulants in preventing stroke in AF patients. However, warfarin treatment is rather inconvenient because of the need for close monitoring, a procedure that requires laboratory tests, blood sampling, dose adjustments and visits to a physician. This implies INR-monitoring to ensure correct level of anticoagulation. In recent years new oral anticoagulants (NOACs), which exert their effects through other mechanisms than vitamin K antagonism, have been introduced. They act by either inhibiting the blood clotting factor thrombin (dabigatran) or the clotting factor Xa (rivaroxaban and apixaban) (6). More drugs belonging to these drug classes are currently being developed and are expected to enter the market in a few years. The NOACs are given in fixed doses and there is no need for laboratory monitoring of the treatment as such. However, there will be a need for regular monitoring of patients with regard to safety and follow-up of their AF.

During the last decade considerable efforts have been made to select those AF patients who should receive antithrombotic therapy. Some AF patients are at low risk of thromboembolic stroke. Together with the fact that antithrombotic management induces some degree of bleeding risk this means that careful patient selection is pivotal. Whereas the immediate stroke risk is low in young and middle-aged patients with lone atrial fibrillation, the risk increases greatly in those with certain risk factors. The CHADS$_2$ score is a tool for estimating the stroke risk in AF patients (7). CHADS$_2$ is derived from **C**ongestive heart failure, **H**ypertension, **A**ge above 75 years, **D**iabetes, and **S**troke (previous stroke or transient ischemic attack), where one point is given for each of the first four conditions and two points for stroke. Thus the maximum score will be six points. A high score corresponds to a high risk while a low score indicates a lower risk. Recently, a refinement of this scoring system has been introduced to better identify patients in the lower risk range. This is the CHA$_2$DS$_2$VASc score, where V refers to **V**ascular disease, for example coronary artery disease, A to **A**ge 65-75 years, and Sc to **S**ex category, which is female gender (8). For assessment of the risk of bleeding in AF patients the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs concomitantly/alcohol abuse) score has been introduced (6). This is a simple calculation where a score of 3 or more indicates high risk, and thus implying that caution and regular review are recommended.

The NOACs have been compared with warfarin in clinical trials and appear to be promising and acceptable alternatives to warfarin for thrombosis prevention in dif-

ferent conditions, of which AF is the one condition with the highest number of patients. In the present report, the first objective is to summarize evidence of efficacy and safety for these new anticoagulants compared to warfarin. The second objective is to create a model which simulates the lives of AF patients on warfarin with regard to health outcomes and costs. The final and main objective is to combine efficacy data on different clinical outcomes and add these to the model, to simulate what we can expect to happen to health outcome and differences in costs if the new anticoagulants replace warfarin as the choice of oral anticoagulant among AF patients.

Introduction to health technology assessment (HTA)

Health technology assessment (HTA) has been defined as "a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe effective, health policies that are patient focused and seek to achieve best value" (9). The basis of an HTA is a systematic review and evaluation of scientific literature on efficacy and safety of different therapeutic interventions or diagnostics. The HTA may also include economic evaluations and a discussion regarding ethical, social, legal and organisational aspects depending on the question under evaluation.

This HTA consists of data from a systematic review of efficacy and safety and an economic evaluation.

Introduction to economic evaluations of health care programmes

The basic task of any economic evaluation is to identify, measure, value and compare costs and consequences of the alternatives being considered. This is normally done in an incremental analysis, which means that the differences in costs between the intervention alternatives are compared with differences in consequences (10). If an intervention has higher effectiveness and lower costs than a comparator, the intervention is said to be dominant and the comparator is dominated. Likewise, if an intervention has lower effectiveness and higher costs than a comparator, the intervention is said to be dominated and the comparator is dominant. In all other cases, results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E} $$

Because the health care sector, as the society in general, is restricted by scarce resources and budget constraints, economic evaluations are tools for decision makers facing questions of how to prioritize and maximize benefits from scarce resources. For an economic evaluation to be meaningful in a decision making process, the

ICER must be judged with regards to a ceiling ratio that reflects the decision maker's maximum willingness to pay (WTP) for a health gain. The decision rule for an economic evaluation can therefore be expressed as:

$$\frac{\Delta C}{\Delta E} < \lambda$$

where λ equals WTP, and means that if the ICER of an intervention is below the ceiling ratio, introducing the intervention represents good value for money. Because the ICER has poor statistical properties, ICERs are often rearranged to express either net monetary benefit (NMB) or net health benefit (NHB), which yields the following decision rules related to NMB or NHB.

$$NMB : \lambda \cdot \Delta E - \Delta C > 0$$

$$NHB \; : \Delta E - \frac{\Delta C}{\lambda} > 0$$

An intervention can in other words be considered cost-effective if it yields a positive NHB or NMB.

Economic evaluations are often based on decision models (such as decision trees, Markov models, etc) that calculate results based on input parameters. There are always uncertainties related to the values of these parameters, making sensitivity analyses an important feature of economic evaluations based on decision models. In short, sensitivity analyses illustrate how much the results vary when model parameters are changed. Sensitivity analyses can be performed in different ways, with one-way as the simplest and most common approach. In one way analyses one model-parameter is changed at a time, while all the other model-parameters are held constant, to see how much impact the variation in this parameter has on the results. One-way sensitivity analyses are often presented as tornado-diagrams, which identify and illustrate the model-parameters that have the highest impact on the results. Sometimes, two way sensitivity analyses are presented, in which two key parameters are simultaneously changed, while the remaining are kept constant.

In addition to the above, it is good practice to present results with probabilistic sensitivity analysis (PSA). PSA is often presented as scatter-plots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane. An advantage of PSA is that it allows to simultaneously taking the uncertainties of model-parameters into account. The basic approach in PSA is to assign appropriate probability distributions to the model-parameters, which makes it possible to replace the "fixed" values of the parameters by values generated by random draws from the distributions. Doing this repeatedly, with a specified number of iterations, makes it possible to estimate the probabilities that alternatives are cost-effective, subject to different ceiling values of WTP. This is usually done for a range of different ceiling values of WTP. PSA may also be presented as cost-effectiveness acceptability curves (CEACs), that show the probability of the alternatives being cost-effective subject to changing

values of WTP. In a CEAC plot, one may highlight the strategies which at each given WTP is the most cost-effective. This figure is usually called cost-effectiveness acceptability frontier (CEAF).

Another useful result that can be extracted from PSA is the expected value of perfect information (EVPI). This is a number which indicate the value to society of having more accurate evidence to inform the decision. If EVPI for a given population seems large, it might be of interest to find out for which parameters it would be most useful to get new and improved data. Expected value of perfect information for parameters is a more time-consuming operation which can give information on which single parameters or groups of parameters it is most cost-effective to conduct new research on.

The Norwegian Knowledge Centre for the Health Services utilize PSA in it's economic evaluations as described above. In short, making a model probabilistic means that it is possible to estimate the uncertainty in the decision of implementing alternative interventions, and indicates the value of collecting additional information from new research.

Priority setting criteria

According to Norwegian policy documents (11;12), a treatment should be prioritized if the following criteria are met:

1. *The disease is severe;* A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual in his or her daily activities. Severity is also evaluated according to the risk increase the disease entails in terms of death, disability and discomfort, if treatment is postponed.

2. *The treatment is effective;* the patient should be expected to benefit from treatment in terms of longevity or improved quality of life of certain duration. The treatment effectiveness should also be well documented.

3. *The treatment is cost-effective;* the added costs of the treatment should be reasonable compared to the added benefits.

The policy documents mentioned above give no guidance as to what constitutes a "reasonable" relationship between costs and effectiveness for a given health intervention. The Directorate of Health however, has recommended a preliminary estimate of NOK 500 000 per statistical life year in full health (13;14). This value was reflects assumptions based on Norwegian kroner in 2005, and translates to 588 000 for 2012 (14). However, there is no consensus regarding this threshold value, nor has it been subject to a political process and can therefore be regarded as nothing

more than a tentative suggestion. The WHO recommendation of using a threshold in the range of 1 to 3 times a country's per capita GDP would result in a threshold between 555 202 and 1 665 606 for Norway in 2011 (15).

Clinical evaluation - Methods

Literature search

Research librarian Ingrid Harboe planned and executed all systematic searches in collaboration with the project group. We searched electronic databases and selected websites. Searches were performed in two steps, first for systematic reviews (SR) and health technology assessments (HTA reports) and secondly for newly published randomized controlled trials (RCT). The search for RCTs was limited to years 2011 and 2012 up to week 11. The complete search strategy, list of databases and websites and explanations are listed in appendix 1.

The Norwegian Medicines Agency and the pharmaceutical companies with marketing authorization for the included interventions were contacted and given the opportunity to supplement our search with non-identified articles or data matching our inclusion criteria.

Inclusion criteria

Population: Patients with non-valvular atrial fibrillation at moderate and high risk of stroke ($CHADS_2 \geq 1$)

Intervention: Dabigatran (110 mg x2 or 150 mg x2)
Rivaroxaban (20 mg x 1)
Apixaban (5 mg x 2)

Comparison: Warfarin to INR 2.5 (2.0-3.0)
Dabigatran (110 mg x2 or 150 mg x2)
Rivaroxaban (20 mg x 1)
Apixaban (5 mg x 2)

Outcome: Mortality (all cause)
Ischemic stroke or systemic embolism
Hemorrhagic stroke / intracranial bleeding
Acute myocardial infarction (AMI)
Major gastrointestinal (GI) bleeding

Major bleeding (not GI or intracranial)
Quality of life (EQ5D, 15D, SF6D, SF36, HUI)

Study design
- HTA reports/Systematic Reviews (SR)
- RCT

Language: No limitations in languages during the search, but we only included articles in English, articles with English abstract and articles in Scandinavian.

Selection of articles

Two persons independently reviewed all citations generated by the search to identify potentially relevant articles based on title and/or abstract. Full text versions were obtained for articles appearing to meet our inclusion criteria or for cases in which sufficient information was not available to make a decision. Two persons independently assessed the relevance of articles according to our list of inclusion criteria. Disagreements were resolved by discussion or by consulting a third party.

Articles meeting the predefined inclusion criteria were assessed for quality according to a check list for systematic reviews or for risk of bias for randomized controlled trials (16). All assessments were performed and agreed upon by two persons.

Data analysis

We extracted data as they were presented in the included publications. When data were presented in several ways, we chose to report data in our preferred order; hazard ratio (HR), relative risk (RR) and odds ratio (OR) with 95% confidence intervals (CI). When the included HTA report did not report data for our pre-specified outcomes, we retrieved the original publications to see if the outcomes were reported there.
All data were extracted by one person, and controlled by a second person for accuracy.

Grading the quality of evidence

Two reviewers assessed overall confidence in the results for each outcome by using GRADE (Grading of Recommendations, Assessment, Development and Evaluation, www.gradeworkinggroup.org). The method is based on the study design used and involves an evaluation of eight criteria for each outcome. Limitations in any of five criteria may lower the quality: study quality/risk of bias, consistency between trials,

directness (in how similar the population, intervention, and outcomes are between the trials and the stated objectives of this report), precision of the estimates and reporting bias. The three criteria to evaluate an increase in quality are: large effect, presence of a dose-response gradient and plausible confounding that would change (lower) the effect.

To perform the evaluation, we used the quality assessments of the randomized controlled trials presented in the included HTA report (17) Finally the overall quality was categorized as high, moderate, low or very low.

GRADE gives the following definition of the different quality of evidence:
High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

Clinical evaluation - Results

Result of literature search

We identified 134 titles in the search for literature (105 SR, 29 RCT) in March 2012. In addition we identified one ongoing drug class review/health technology assessment (HTA) (17) and a guideline (18). A final version of the HTA was available in time to be used in our project.

We reviewed the identified literature and found 20 references to be potentially relevant for our purpose and full text copies were reviewed. Finally, one comprehensive HTA report met our pre-specified inclusion criteria (fig. 1).

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┌─────────────────────────┐
│ 136 identified references from │
│      literature search       │
└─────────────────────────┘            ┌──────────────────────────┐
            │                          │ 116 references excluded       │
            │                          │ on the basis of title and abstract │
            ▼                          └──────────────────────────┘
┌─────────────────────────┐
│ 8 SR, 10 RCT, 1 HTA, 1 Guideline │    ┌──────────────────────────┐
│     evaluated in full text      │    │ 19 references excluded        │
└─────────────────────────┘            │ (study design, already included in │
            │                          │ SR/HTA, newer/more comprehensive  │
            │                          │       data available)          │
            ▼                          └──────────────────────────┘
┌─────────────────────────┐
│   1 study quality evaluated   │       ┌──────────────────────────┐
└─────────────────────────┘            │ 0 studies excluded            │
            │                          │ on the basis of quality evaluation │
            │                          └──────────────────────────┘
            ▼
┌─────────────────────────┐
│      1 HTA included          │
└─────────────────────────┘
```
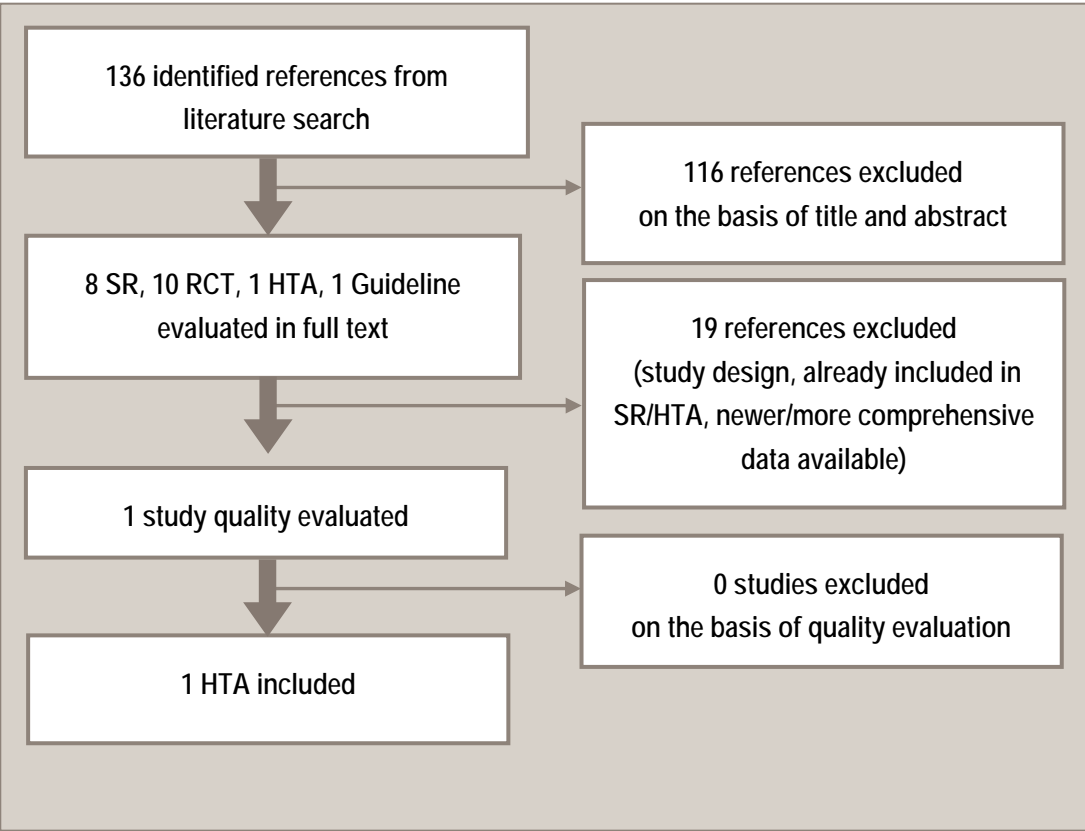
Figure 1 *Flowchart of identification of documentation.*

Description of the included documentation

Short description of the included HTA report

The included HTA report from CADTH, "Safety and Effectiveness of New Oral Anti-coagulants Compared to Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation", investigated the use of apixaban, dabigatran, rivaroxaban and warfarin in patients with atrial fibrillation (17). They performed a systematic review following procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions (19), a network meta-analysis for the three new oral anticoagulants for specified outcomes and an economic evaluation.

Their primary research questions were:

"*In patients with non-valvular AF:*
- *What is the clinical effectiveness and safety of new oral anticoagulants compared with warfarin?*
- *What is the cost-effectiveness of new oral anticoagulants compared to warfarin?*
- *How do the new oral anticoagulants compare to optimal warfarin therapy when considering the time spent in the time in therapeutic range (TTR)?*
- *How do the new oral anticoagulants compare to warfarin therapy in specific groups of patients with older age, other medical conditions, or who are taking other drug therapies?*
- *What are the costs associated with warfarin when patients are stratified according to TTR? How do these compare with estimates for the new oral anticoagulants?*
- *What is the cost-effectiveness of new oral anticoagulants compared to warfarin when stratified by age and CHADS2 score?*"

Their search for literature was performed in December 2011 and January 2012. They aimed to include RCTs and non-randomized studies with comparative control group and treatment period of at least 12 weeks. The authors included five unique RCTs with a total of 51 302 patients. The studies have been reported in 15 publications. The three largest studies were multicentre studies performed worldwide. We rated the systematic review part of the HTA to be of high quality.

The following studies were included in the HTA report: ARITOTLE, ARISTOTLE-J, RE-LY, PETRO and ROCKET-AF. All studies used dose-adjusted warfarin as comparator. Short descriptions of the study characteristics are presented in Table 1. There is some heterogeneity between studies, especially regarding baseline risk of stroke (assessed with $CHADS_2$ score) and study duration, as can be seen in Table 1.

Table 1 Characteristics of the studies included in the HTA-report (17)

Trial	Intervention Comparator	Study size and duration of follow-up	Patient characteristics (across randomized groups)	Comments
ARISTOTLE	Apixaban 5mg bid† (2.5mg bid for selected patients, N=428) Warfarin	N=18 201 (approx. 1:1) Max.4 years Median follow-up 1.8 years	Age^:70,0 Male (%):64,5-65,0 $CHADS_2$*:2,1-2,1 ASA‡ at baseline (%):30,5-31,3 Warfarin naïve(%):42,8-42,9	$CHADS_2$ of 1: 34% (excluded patients with score 0)
ARTISTOTLE-J	Apixaban 5mg bid Apixaban 2.5mg bid Warfarin	N=222 (approx. 1:1:1) Max.12 weeks Median duration on treatment 85 days	Age*:69,3-71,7 Male (%):81,1-85,1 $CHADS_2$*:1,8-2,1 ASA use during study (%):20,8-28,2 Warfarin naïve(%):12,7-16,0	Single country: Japan
RE-LY	Dabigatran 110mg bid Dabibatran 150mg bid Warfarin	N=18 113 (approx.1:1:1) Max.3 years Median follow-up: 2 years	Age*:71,4-71,6 Male (%):63,2-64,3 $CHADS_2$ *:2,1-2,2 ASA at baseline *(%):38,7-40,6 Warfarin naïve(%):49,8-51,4	$CHADS_2$ of 0 and 1: 32% of patients
PETRO	Dabigatran 50mg bid Dabigatan 300mg bid Dabigatran 150mg bid Warfarin	N=502 (D150mg=166, W=70, D50mg/D300mg= 236 not reported here) Maximum 12 weeks on treatment	Age^:69-70 Male (%):81,3-84,3 $CHADS_2$*:Not Reported ASA at baseline (%):Not Reported Warfarin naïve(%):0	Dose-finding study aimed at safety investigation
ROCKET-AF	Rivaroxaban 20mg (15mg if cCl 30-49mL/min) Warfarin	N=14 264 (approx. 1:1) Max.4 years Median follow-up: 1.9 years	Age^:73,0 Male (%):60,3 $CHADS_2$*:3,46-3,48 ASA at baseline (%):38,3-38,7 Warfarin naïve(%):37,5-37,7	Excluded patients with $CHADS_2$ of 0 and 1. Patients with $CHADS_2$ of 3 or higer: >85%

Warfarin: dosed to target INR range 2-3.

* mean

^ median

† bid = twice daily

‡ASA = Acetylsalisylic acid (aspirin)

Presentation of results from direct comparisons

The HTA report presented the results from direct comparisons in the included studies (17). The authors have described the definition of the outcomes across studies to make it easier to compare. We present data as they appear in the HTA report. The outcomes ischemic stroke or systemic embolism, major bleeding not intracranial or gastrointestinal and quality of life were not reported. We therefore assessed the original publications of the studies included in the HTA report and we were able to extract data regarding ischemic stroke.

We used the risk of bias evaluations performed by the authors of the HTA report. The authors generally noted unclear or high risk of bias for items like incomplete outcomes addressed and other bias. We assessed quality of the evidence to range from low to very low due to limitations in study design, unclear reproducibility and wide confidence intervals (see appendix 3 for details).

The results in Table 2 are presented as hazard ratio and 95% confidence intervals compared to warfarin. The efficacy results are limited to data reported in ARISTOTLE (20), RE-LY (21) and ROCKET-AF (22), which are all large and confirmatory phase 3 trials.

Table 2 Individual study results, reported as HR with 95% CI, compared to warfarin

	ARISTOTLE (apixaban)	RE-LY (dabigatran***)	ROCKET-AF (rivaroxaban)
All cause mortality	0.89 (0.80-1.00)	D110: 0.91 (0.80-1.03) D150: 0.88 (0.77-1.00)	0.92 (0.82-1.04)
Ischemic stroke or systemic embolism*	Ischemic or uncertain stroke: 0,92 (0,74-1,13)	Ischemic or uncertain stroke: D110:1,11 (0,89-1,4), D150:0,76 (0,6-0,98)	Ischemic stroke (in as treated safety population): 0,94 (0,75-1,17)
Intracranial bleeding	0.42 (0.30-0.58)	D110: 0.31 (0.20-0.47) D150:0.40 (0.27-0.60)	0.67 (0.47-0.93)
Acute myocardial infarction	0.88 (0.66-1.17)	D110:1.35 (0.98-1.87) D150:1.38 (1.0-1.91)	0.81 (0.63-1.06)
Major gastrointestinal bleeding **	0.89 (0.70-1.14)	D110:1.10 (0.86-1.41) D150:1.50 (1.19-1.89)	1.60 (1.29-1.98)
Major bleeding, not gastrointestinal or intracranial	Not reported	Not reported	Not reported
Quality of life	Not reported	Not reported	Not reported

*Data for ischemic stroke retrieved from original publications,

**GI bleeding was not explicitly defined across all studies included in the HTA.

***Dabigatran analysed in two different doses (110 mg and 150 mg)

Subgroups reported in the HTA report were by age (over and under 75 years), time in therapeutic range, TTR (over and under 66%) and CHADS$_2$ (over and below score 2) for the primary outcomes of all-cause stroke or systemic embolism and major bleeding. However, we were not able to disentangle data for our other predefined outcomes.

Presentation of results from network meta-analyses

The authors of the included HTA report performed a Bayesian fixed-effects network meta-analysis (17). This is an analysis combining studies through both direct and indirect evidence. This analysis was restricted to the three large phase 3 studies, ARISTOTLE, RE-LY and ROCKET-AF, since there were zero events in both arms for many of the outcomes in the other identified studies. Warfarin served as the chosen reference group.

The report presents data for all cause mortality, intracranial bleeding, major GI bleeding and myocardial infarction (see Table 3). We have not performed additional network analyses for our endpoints of ischemic stroke or systemic embolism, hemorrhagic stroke / intracranial bleeding, major bleeding (not GI or intracranial) or quality of life.

Table 3 Results from network meta-analyses, OR (95% CrI) for apixaban, dabigatran and rivaroxaban versus warfarin.

	All cause mortality	Intracranial bleeding	Major GI bleeding	Myocardial infarction
Apixaban vs warfarin	0.90 (0.80-0.998)	0.42 (0.30-0.58)	0.88 (0.68-1.15)	0.88 (0.66-1.17)
Dabigatran 110mg vs warfarin	0.91 (0.8-1.05)	0.30 (0.19-0.45)	1.08 (0.84-1.40)	1.32 (0.98-1.79)
Dabigatran 150mg vs warfarin	0.89 (0.78-1.01)	0.42 (0.28-0.60)	1.45 (1.14-1.86)	1.29 (0.96-1.75)
Rivaroxaban vs warfarin	0.93 (0.83-1.04)	0.66 (0.47-0.92)	1.61 (1.30-1.99)	0.80 (0.62-1.05)*
Dabigatran 110mg vs apixaban	1.03 (0.86-1.22)	0.71 (0.41-1.21)	1.23 (0.85-1.78)	1.50 (0.99-2.28)
Dabigatran 150mg vs apixaban	1.00 (0.84-1.19)	0.99 (0.60-1.62)	1.65 (1.16-2.38)	1.47 (0.97-2.23)
Rivaroxaban vs apixaban	1.04 (0.89-1.23)	1.56 (0.97-2.5)	1.83 (1.30-2.57)	0.92 (0.62-1.35)
Dabigatran 150mg vs dabigatran 110mg	0.97 (0.85-1.12)	1.41 (0.86-2.33)	1.35 (1.07-1.72)	0.98 (0.74-1.31)
Rivaroxaban vs dabigatran 110mg	1.02(0.86-1.21)	2.22(1.29-3.89)	1.49(1.07-2.09)	0.61(0.41-0.91)
Rivaroxaban vs dabigatran 150mg	1.05(0.88-1.26)	1.58(0.95-2.66)	1.11(0.8-1.53)	0.63(0.42-0.93)

* safety on treatment value

Economic evaluation - methods

General

We performed a cost-utility analysis (CUA) where relevant costs are expressed in 2012 Norwegian kroner (NOK) and effects are expressed in quality-adjusted life-years (QALYs). The analysis is performed from a health care perspective and both costs and effects are discounted with an annual discount rate of 4% as recommended by the Norwegian Ministry of Finance, Norwegian Medicines Agency and Norwegian Directorate of Health (14;23;24).

Results are presented as mean incremental cost-effectiveness ratio (ICER) and mean net health benefits (NHB) from 1000 runs of the model in base case. In the absence of an explicit threshold value for cost-effective interventions in Norway, we assume a value of NOK 588 000 per QALY gained, as recommended by the Norwegian Directorate of Health as a tentative estimate (14). The use, size and possible range of a threshold value is currently under discussion (25).

Uncertainties in model-parameter inputs are handled by a probabilistic sensitivity analysis, and by performing one-way sensitivity analyses on key parameters.

Model structure

We designed a Markov model with 8 Markov states and a life-time perspective. Base case cycle length in the model is 12 months. Because more than one event can happen during a year, the model was also set up to faclitate analyses with one month cycles. This approach may, however, produce spurious results (26), hence monthly cycles were used only as a sensitivity analysis. The eight Markov states were defined as atrial fibrillation (AF), heart failure, moderate stroke sequela, severe stroke sequela, dead and atrial fibrillation with previous AMI, stroke or major gastrointestinal bleeding. In Figure 1 we present the possible transitions between the states:

Figure 1 Model structure (arrows represent health events, while boxes are health states)
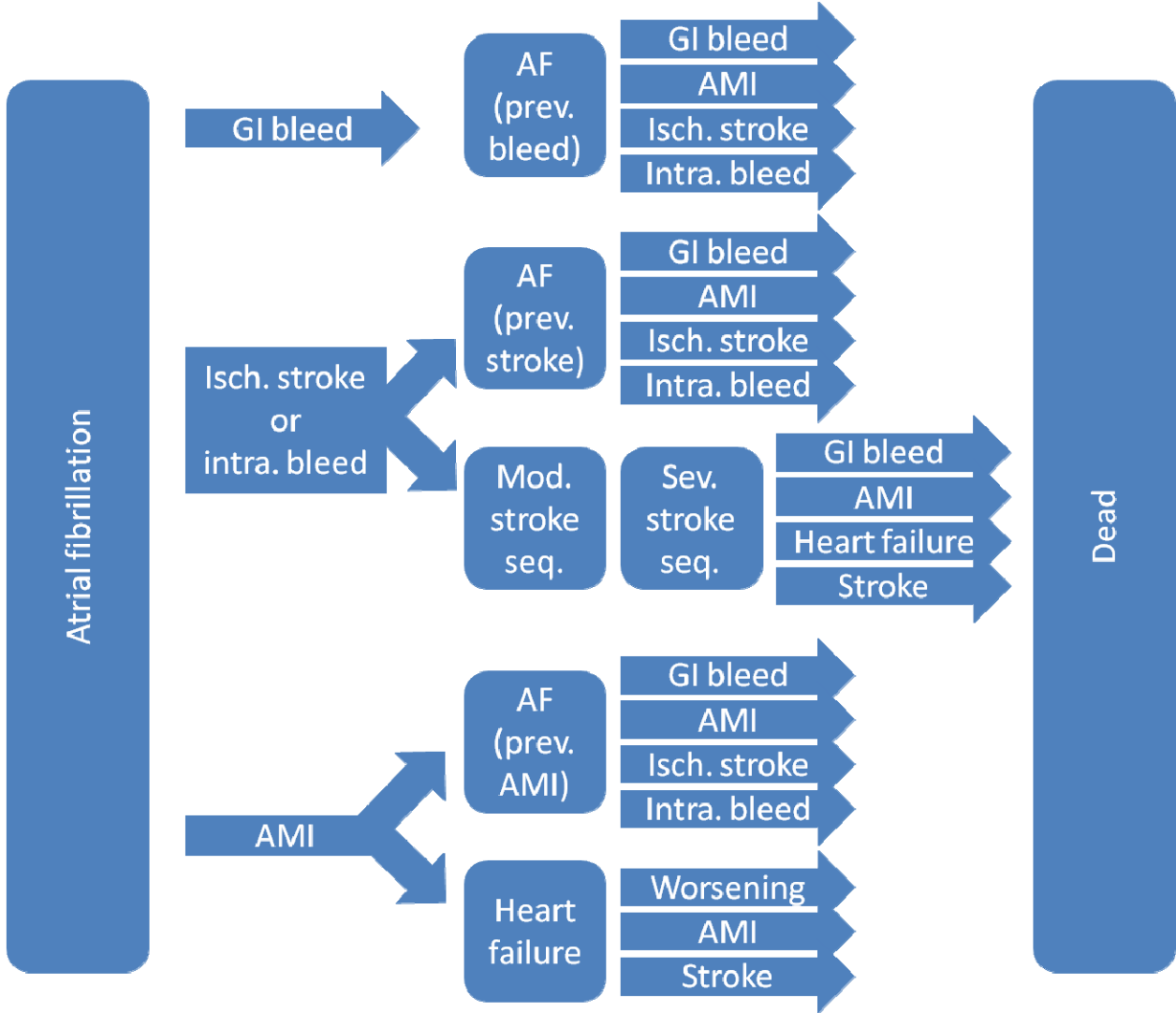
In addition, the risk of death was present in all health states. All nodes for which more than one event was possible, were split into binary choices in order to avoid the possibility of probabilities becoming more than 1 or less than 0 in the probabilistic analyses.

The health states "moderate" and "severe stroke sequela" were defined as dependent stroke patients who were living outside or inside nursing homes, respecitvely. Patients who were independent after a stroke were assumed to be in the health state "AF with previous stroke". Similarly, "AF with previous bleeding" and "AF with previous AMI" are patients who have more or less recovered from these serious events.

The model was designed to compare any oral anticoagulant versus another, provided that efficacy data are available. Hence, this model can easily be used for new interventions not already included in this report. All individuals started in the health state "atrial fibrillation", and were propagated through the model based on transition probabilities estimated from epidemiological clinical, effectiveness and cost data considered to be the best available for Norway.

Model parameters

Most parameters in the model are uncertain and were thus included as probability distributions in order to facilitate probabilistic sensitivity analyses. Each distribtution type is specified in the following sections . More detailed information about types of distributions can be found in textbooks.

Epidemiology

All probabilities are incorporated into the model as beta distributions and all relative risks and hazard ratios are lognormal distributions. Beta distributions were fitted using the integers events and at risk. Lognormal distributions were fitted using the log of mean and the standard error of this log of the mean.

Probabilities of initial events (baseline clinical data)

Based on principles for evidence based decision modelling, we wanted to include epidemiological data from sources within the "jurisdiction of interest" (27). We searched Embase and Medline with search terms appropriate for each of the events for epidemiological data containing probabilities of events. If Norwegian data were unavailable we considered other Scandinavian registries as the most relevant input. Based on these searches, all probabilities of events for patients with atrial fibrillation were based on registries from Scandinavia. In addition, one international registry was used for two data inputs for which we lacked Scandinavian data. All rates from studies were transformed into transition probabilities for use in the model.

Probability of having ischemic stroke by varying CHA_2DS_2-VASc-score was based on a Swedish registry (8). The registry data was divided into the 10 different CHA_2DS_2-VASc groups (Table 4). These ischemic strokes and persons at risk were fitted into beta distributions. The average follow-up in the registry was 1.5 years, which may be too limited a time frame, considering that the model has a life-time perspective. Based on a Danish registry (28), we computed that the risk of having an ischemic stroke in years 2 to 10 after initial diagnosis of atrial fibrillation was reduced by 35% in later years as compared to the initial years.

Table 4 Rates of ischemic stroke

CHA$_2$DS$_2$-VASc	Ischemic strokes	At risk	Estimated risk first year	Estimated risk later years
0	11	5343	0.002	0.001
1	41	6770	0.006	0.004
2	247	11240	0.022	0.014
3	566	17689	0.032	0.021
4	916	19091	0.048	0.031
5	1043	14488	0.072	0.047
6	929	9577	0.097	0.063
7	500	4465	0.112	0.073
8	168	1559	0.108	0.071
9	33	268	0.122	0.080

Incidence rates for ischemic stroke were adjusted according to age based on data from a Danish registry (29). Relative risks of stroke were calculated from incidence in each age group divided by the average in age groups 65-74 and 75+ (Table 5). This approach assumes that the average age in the data forming Table 4 (approx. 76 years) equals the average age in the two mentioned age groups.

Table 5 Age adjustment of ischemic stroke incidence

Age	RR*	Ln(RR)**	SE***
20-44	0.0062	-5.0862	0.1864
45-54	0.0494	-3.0078	0.1217
55-64	0.1872	-1.6755	0.0681
65-74	0.4738	-0.7469	0.0565
75+	1.4466	0.3692	0.0359

*RR is relative risk of event relative to the average (the other two columns are input into probability distributions)

**Ln = natural logarithm

***SE = Standard error

Probability of intracranial bleeding was based on the same registry as ischemic stroke (8). We used data for the subgroup of patients who had received oral antico-agulants[1]. The data was divided according to HAS-BLED-score as shown in Table 6.

---

[1] For HAS-BLED=0, calculations were based on an average of all groups due to few data.

Table 6 Risk of intracranial bleeding

HAS-BLED	Intracranial bleeding	At risk	Estimated annual risk of intracranial bleeding
0	1	2696	0.00021
1	21	10563	0.00200
2	113	18785	0.00600
3	98	14032	0.00700
4	57	4729	0.01200
5	10	625	0.01600

Probability of intracranial bleeding was adjusted according to age analogously to probability of ischemic stroke (Table 7). In addition, data from a Danish registry (28) were used to adjust incidence rates according to CHA_2DS_2-VASc-score (Table 8).

Table 7 Age-adjustment of incidence of intracranial bleeding

Age	RR*	Ln(RR)**	SE***
20-44	0.0204	-3.8934	0.2760
45-54	0.1677	-1.7855	0.1823
55-64	0.2968	-1.2146	0.1479
65-74	0.5219	-0.6502	0.1437
75+	1.4057	0.3406	0.0961

*RR is relative risk of event relative to the average (the other two columns are input into probability distributions)

**Ln = natural logarithm

***SE = Standard error

Table 8 Adjustment of intracranial bleeding risk based on CHA_2DS_2-VASc-score

CHA_2DS_2-VASc	RR*	ln(RR)	SE(ln(RR))
0	0.1040	-2.2637	0.2900
1	0.2679	-1.3171	0.1524
2	0.4945	-0.7042	0.0933
3	0.7891	-0.2369	0.0684
4	1.2356	0.2116	0.0617
5	2.0340	0.7100	0.0607
6	2.6312	0.9674	0.0734
7	2.8657	1.0528	0.1160
8	2.9830	1.0929	0.2483
9	3.1510	1.1477	0.6203

*RR is relative risk of event relative to the average (the other two columns are input into probability distributions)

**SE (standard error) is calculated based on (28) and (29)

Probability of major gastrointestinal bleeding was based on Danish registry data which reported an incidence rate of 0.009 gastrointestinal bleedings per patient year (30). This rate is somewhat lower than the included clinical trials, which reported rates between 0.013 and 0.020 for patients on warfarin. The rate was adjusted for varying CHA2DS2-VASc-score and HAS-BLED-score according to Swedish (8) and Danish (31) registry data respectively (Table 9).

Table 9 Adjustment of major gastrointestinal bleeding risk based on HAS-BLED and CHA$_2$DS$_2$-VASc-score

HASBLED	RR*	ln(RR)	se(ln(RR))
0	0.05520	-2.89673	0.59730
1	0.37104	-0.99144	0.12016
2	1.00712	0.00709	0.06131
3	1.27215	0.24071	0.06252
4	1.80221	0.58901	0.08377
5	3.02135	1.10570	0.16571
6	8.21595	2.10608	0.34591
7	8.80417	2.17523	1.66404
CHA$_2$DS$_2$-VASc	RR*	ln(RR)	se (ln(RR))
0	0.61	-0.4947	0.0536
1	0.79	-0.2299	0.0383
>=2	1.12	0.1116	0.0205

*RR is relative risk of event relative to the average (the other two columns are input into probability distributions

Probability of acute myocardial infarction was based on a Norwegian registry (32), reporting risk in a general population. These data are also reported in a previous report from NOKC (NorCaD, (33) Table 10). These data were multiplied by a factor of 1.23 to mimic an AF population, based on a large international registry study (34).

Table 10 Yearly risk of acute myocardial infarction (AMI) in Norway

Age	Risk of AMI
40	0.000940605
50	0.002115584
60	0.004407182
70	0.008501229
80	0.013862216
90	0.016855004

Mortality for patients with atrial fibrillation (AF) was based on 2011 Norwegian mortality data from Statistics Norway (www.SSB.no) (see table in Appendix 4). These mortality data were multiplied by relative risks of death for AF patients from a Swedish registry (Table 11) (35).

Table 11 Hazard ratio for dying with AF compared to no AF

Age	Hazard ratio (HR)	ln(HR)	SE(ln(HR)
<65	3.14	1.15	0.04
65-74	2.31	0.84	0.02
>=75	1.71	0.54	0.01

In addition, mortality was adjusted by CHA$_2$DS$_2$-VASc-score based on a Danish registry (Table 12) (28).

Table 12 Relative risk of death by varying CHA$_2$DS$_2$-VASc-score

CHA$_2$DS$_2$-VASc	RR*	ln(RR)	se(ln(RR))
0	0.1859	-1.6827	0.0443
1	0.3955	-0.9276	0.0249
2	0.8113	-0.2091	0.0138
3	1.0370	0.0363	0.0110
4	1.1991	0.1816	0.0110
5	1.5118	0.4133	0.0115
6	1.7230	0.5441	0.0141
7	1.9591	0.6725	0.0208
8	2.9792	1.0917	0.0252

*RR is relative risk of event relative to the mean in the study (28) (the other two columns are input into probability distributions)

We estimated the increased risk of heart failure among AF patients to be 3.04 (2.77-3.33). This increased risk was based on an international registry (34), multiplied by the risk of heart failure in the Norwegian population, which was estimated from the HKS study (32) for the NorCaD model (33). In addition, patients are at risk of developing heart failure when they experience an AMI. Data on this is based on a Swedish registry (36).

Probability of subsequent events

Probability of dying for patients with heart failure is based on a recent Norwegian study which reported the adjusted hazard ratio to be 1.037 (0.901-1.193) for patients with heart failure and AF compared to patients with only AF (37). This hazard ratio was applied to the AF mortality risk for patients with heart failure.

Hazard ratio for death after stroke was based on a Swedish registry of 105 074 patients comparing mortality for the 30% who had atrial fibrillation with the 70% who had no atrial fibrillation. The hazard ratio of 1.24 (1.20-1.28) was applied to the overall mortality for AF patients.

Probability of severe and moderate stroke sequelae was based on Swedish registry data (38) (Table 13).

Table 13 Percentage in different sequelae after stroke

Age	Severe sequelae	Moderate sequelae
<75	10.5 %	30.0 %
>=75	20.0 %	48.5 %

Patients who experienced stroke had an increased probability of a new stroke based on the increase in their CHA_2DS_2-VASc and HAS-BLED scores which is 2 points higher in CHA_2DS_2-VASC and 1 point higher in HAS-BLED.

The probability of AMI in patients with moderate stroke sequelae was based on calculations done for the NorCaD model and based on a meta-analysis of data from two different registries (39;40) in which the relative risk of AMI in stroke patients was estimated to be 4.3 (3.9-4.6) compared to the general population. In the model, this relative risk was multiplied by the incidence of AMI reported in the general population as used in NorCaD (33).

The probability of AMI in heart failure patients was based on a Dutch registry, reporting that the hazard ratio of a non-fatal cardiac event was 2.6 (1.4-4.7) for heart failure patients compared to participants without heart failure (41). This hazard ratio was multiplied by the overall incidence of AMI in the general population to give estimated risk of AMI for heart failure patients.

Probability of stroke was assumed to be the same for patients with and without heart failure.

Bleeding for patients with moderate stroke sequelae or heart failure was based on Danish registry data (42). The relative risk of bleeding was estimated to be 1.27 (1.15-1.40) and 1.22 (1.11-1.35) for stroke patients and heart failure patients, respectively. These relative risks were incorporated into the model as lognormal distributions and attached to the risks of bleeding for AF patients.

For the health states AF with previous AMI, stroke or major gastrointestinal bleeding, the risk of events was increased according to the corresponding increase in CHA_2DS_2-VASC and HAS-BLED score. Hence, an AMI resulted in 1 point higher CHA_2DS_2-VASC and no point higher HAS-BLED score. A stroke resulted in 2 points higher CHA_2DS_2-VASC and 1 point higher HAS-BLED score. And finally a major gastrointestinal bleeding resulted in no point higher CHA_2DS_2-VASC and 1 point higher HAS-BLED score.

For patients with heart failure, the risk of worsening of heart failure was estimated as in NorCaD, based on EuroHeart data to be 0.124 (43).

Clinical efficacy parameters in the model

Distributions for clinical efficacy parameters were based on the clinical evaluation part of this report. All efficacy parameters were based on the hazard ratios from the studies, as reported in Table 2 in "Clinical evaluation – Results". All efficacy parameters were added into the model as lognormal probability distributions with standard errors of the logarithm calculations based on the reported confidence intervals (Table 14). Our intention when starting this project was to base efficacy estimates on the network meta-analysis of the included trials. A network meta-analysis does however not add much compared to using the efficacy estimates directly from trials when all these have one common comparator. In addition, hazard ratios were reported in the trials, while odds ratios were reported in the network meta-analysis. Hazard ratios are calculated based on continuous reporting during trials, while to odds ratios are calculated based only on observations from the end of the trials. Due to both these facts, we decided to use the hazard ratios from trials in the model (Table 14).

Table 14 Efficacy from included trials

	Apixaban *vs* warfarin			Dabigatran 110 *vs* warfarin			Dabigatran 150 *vs* warfarin			Rivaroxaban *vs* warfarin		
	RR	ln(RR)	SE	RR	ln(RR)	SE	RR	ln(RR)	SE	RR	ln(RR)	SE
All cause mortality	0.89	-0.12	0.06	0.91	-0.09	0.06	0.88	-0.13	0.07	0.92	-0.08	0.06
Ischemic or uncertain stroke *	0.92	-0.08	0.11	1.11	0.10	0.12	0.76	-0.27	0.13	0.94	-0.06	0.11
Intracranial bleeding	0.42	-0.87	0.17	0.31	-1.17	0.22	0.40	-0.92	0.20	0.67	-0.40	0.17
Acute myocardial infarction	0.88	-0.13	0.15	1.35	0.30	0.16	1.38	0.32	0.16	0.81	-0.21	0.13
Major gastrointestinal bleeding	0.89	-0.12	0.12	1.10	0.10	0.13	1.50	0.41	0.12	1.60	0.47	0.11

*Data taken from original RCT articles, not from included HTA report

Warfarin has been in use for decades, and INR-monitoring for it's users is well integrated with the practice of Norwegian GPs. Norwegian warfarin users are relatively well controlled, being within the recommended INR-range approximately 70% of the time (3), a result that is somewhat higher than what is observed in the included trials. Warfarin users may therefore have a better prognosis in a Norwegian "real life

setting" than in the trials, which implies that the incremental effectiveness of the new anticoagulants compared to warfarin may be smaller in Norway than what is observed in the trials. This possibility is supported by analyses by Wallentin et al. (44), where dabigatran seems to be less effective compared to warfarin with increasing percentage of patients within INR-range. To account for this discrepancy, we conducted subgroup analyses with efficacy input according to the group with INR control closest to what is assumed for Norway (group 3 in RE-LY re-analysis by Wallentin).

Follow-up in the three RCTs was approximately three to four years (3.2 in RE-LY, 3.4 in ROCKET-AF and 4.1 in ARISTOTLE). In the model, costs and effects of the interventions are assumed for the entire remaining lifetime. In sensitivity analyses, we explored to what extent, as recommended for warfarin (45), stopping the use of the intervention drugs when the patient experienced a serious adverse event influenced the results.

Costs

All oral anticoagulants are recommended for the remainder of a person's life, unless side effects or other problems are detected. Hence, costs and effects were assumed to last until death or age 105 years old, with some adjustment for adherence in sensitivity analyses. Gamma or lognormal distributions were applied for all cost parameters.

We assumed that the average dose of warfarin was 5 mg per day, based on Swedish registry data (46). This dose was also used by Boehringer-Ingelheim when applying for reimbursement in Norway (3). For the new oral anticoagulants, we assumed that the average dose of rivaroxaban was 1 x 20 mg. The recommended dose of dabigatran is 2 x 150 mg per day for patients aged below 75 (according to ESC) or 80 (according to NoMA). For older patients, the recommended dose is 2 x 110 mg. We performed analyses with three different dabigatran scenarios; 2 x 110 mg for all ages. 2 x 150 mg up to 75 years (2 x 110 mg thereafter) and 2 x 150 mg up to 80 years (2 x 110 mg thereafter). The three scenarios are termed dabigatran 110, dabigatran 150 ESC and dabigatran 150 NoMA, respectively. Of the three included drugs, apixaban is the only which is not yet approved for reimbursement in Norway. The recommended dose of apixaban is 5 mg x 2 per day. The 5 mg pill got a price just before publishing this report. Whether this price will stay the same in the coming months, and whether any of the other drugs will change their price is unclear. The costs of these drugs are listed in table 15.

Table 15 Costs (NOK) of investigated drugs (per 19.02.2013)

Interventions	Pills per day	Dosage	Price	Pills per package	Price per pill	Price per day	Price per year
Apixaban	2	5 mg	2149.10	168	12.79	25.58	9345
Dabigatran	2	110 mg	753.6	60	12.56	25.12	9175
Dabigatran	2	150 mg	753.6	60	12.56	25.12	9175
Rivaroxaban	1	20 mg	2181.1	100	21.81	21.81	7966
Warfarin	2	2.5 mg	123.4	100	1.23	2.47	901

Patients on warfarin require close monitoring of INR (as mentioned earlier). For Norway, the average number of INR-tests per AF patient per year has been assumed to be approximately 13 (3). A single GP practice has reported this to be 9.2 (47) while a Swedish study has reported average INR-tests per year of 16.2 (48). We incorporated 13 as our estimate, assuming that the distribution varied from 9.2 to 16.2.

The cost of each INR-test has been calculated by several (3;48;49). We used as base-case unit costs the estimates of the NoMA report (3) which calculated INR-testing to cost NOK 368 per visit. We assumed that total health care costs could, at most, be what Björholt calculated for Sweden (NOK 550), which we used as the upper limit of a confidence interval. The cost calculated by Björholt was used by Boehringer-Ingelheim in their reimbursement application to NoMA for dabigatran (3).

For patients on new oral anticoagulants (dabigatran, rivaroxaban or apixaban), NoMA assumed 5 GP visits per year. We also elicited two expert opinions regarding number of visits and based our calculation on the average of these three conjectures, which was 4.17. The cost of these GP visits was assumed to be equal to the cost of the visits for INR-testing, subtracted the cost of the INR test of NOK 69 (same approach as NoMA).

Costs for events and health states are based, to a great extent, on the NorCaD report (33). These costs were updated to 2012 costs. In addition, some events not included in NorCaD were assumed to be based on DRG weights for 2012 (50). Costs are presented in Tables 16 and 17.

Table 16 Event costs

Description	Cost	Source
Cost per acute myocardial infarction	161 898	NorCaD updated
Cost of developing heart failure	13 072	NorCaD updated
Cost per intracranial bleeding	208 634	NorCaD updated
Cost per ischemic stroke	208 634	NorCaD updated
Cost of major GI bleeding	50 923	DRG+transport
Cost of worsening of heart failure	44 334	NorCaD updated

Table 17 Health state costs

Description	Yearly cost	Source
Cost of heart failure per cycle	37 700	NorCaD updated
Cost per year of having moderate stroke sequelae	67 301	NorCaD updated
Cost of having severe stroke sequelae per cycle	946 008	NorCaD updated

Quality of Life

In order to obtain QALY weights we searched for published values. We had prior knowledge of one study eliciting preferences among stroke patients in a Norwegian setting (51).

For consistency and acknowledging that different utility instruments will yield different results, we sought values for all health states and events elicited with the same instrument. We achieved this by choosing values from the EQ-5D (the instrument preferred by NICE for its single technology assessments (52)).

Among several available EQ-5D values, we chose Norwegian values when possible. As the values were not very different across sources the choice was unlikely to influence conclusions. However, we chose not to use values from the Norwegian study to inform values for ischemic stroke, as the different stroke types included there (TIA, ischemic stroke, hemorrhagic stroke) are likely to influence quality of life to different degrees (51).

QALY weights in the model are either attached to longitudinal health states or to short term events that move patients between health states. All patients in this model have atrial fibrillation and are thus in less than perfect health, reflected by their assumed average QALY weight of 0,779 (53). If events happen to them and their health deteriorates, they move to less desirable health states with lower attached QALY weights. Events will thus first lead to temporary reductions in quality of life, and subsequently to QALY loss from moving to a more severe health state. QALY weights assigned to health states are displayed in Table 18 and weights assigned to events in Table 19. Beta distributions were used for all health state and event utilities in the model.

Table 18 QALY values in health states

Health state	QALY weight	SE	Method of elicitation	Reference
Atrial fibrillation	0.779	0.004585	EQ-5D	Berg et al. 2010(53)
Heart failure	0.66	0.10	EQ-5D	Lunde et al. 2012 (51)
Moderate stroke sequela	0.75	0.04	EQ-5D	Lunde et al. 2012 (51)
Severe stroke sequela	0.44	0.09	EQ-5D	Lunde et al. 2012 (51)
Death	0			Per definition

All QALY values for health states were added as multipliers to atrial fibrillation because patients in other health states still have atrial fibrillation. Values displayed in Table 18 represent these multipliers, and not QALYs of being in each health state.

Table 19 QALY values related to health events

Events	QALY weight	SE	Method of elicitation	Reference
Major GI bleed	0.45	0.007947	EQ-5D	Leontiadis et al. 2007 (54)
Intracranial bleeding	0.70	0.013608	EQ-5D	Lee et al. 2010 (55)
AMI	0.71	0.076	EQ-5D	Lunde et al. 2012 (51)
Ischemic stroke	0.80	0.013608	EQ-5D	Lee et al. 2010 (56)

Events were modelled similar to health states, but additionally adjusted for duration of the event, because it is not reasonable to assume the QALY loss for a whole period. Based on expert judgments we assume that all QALY values for events last for 9 to 24 days.

Compliance/adherence

Some concerns have been raised regarding compliance with the new oral anticoagulants (57). One concern seems to be that some of the NOACs have poorer adherence than warfarin in trials. It is, however, likely that this is already captured in the efficacy estimates. We also believe that there is not much decrease in adherence during the years beyond the study periods. This is supported by a Danish registry which have data indicating that there is little difference in warfarin compliance one year and ten years after initiation of treatment (58).

A second concern is that patients were better monitored on NOACs in trials compared to what is expected in real life. Hence, we have performed sensitivity analyses with decreasing effectiveness of NOACs over time to account for decreasing compliance. In these sensitivity analyses, we assumed a quarterly reduction in effectiveness of 6% based on the EuroHeart survey (59). This corresponds well with other data on compliance for warfarin and oral anti diabetics, with 23% and 28% non-adherent (60;61).

Budget impact

In Norway there are probably between 65 000 and 82 000 patients with AF (3). Dabigatran and rivaroxaban are to some extent already in use in Norway, probably mainly for the indications which were approved first. Dabigatran and rivaroxaban are reimbursed for atrial fibrillation from the beginning of 2013, making it likely that the use of these drugs will increase. The extent of this increase will depend on

several factors, including the new guidelines for atrial fibrillation, the relative drug prices, whether NoMA approves reimbursement of apixaban and probably also this report. The extent to which each of these factors will influence use is still unknown, and will greatly depend on the degree of concordance among these factors.

In their application to NoMA, the producer of dabigatran estimated that approximately NOK 55 million would be used on dabigatran five years after the application (3). At a meeting for the Norwegian council for priority setting in health care the total cost of these drugs was indicated to be considerably higher. If we assume that all AF patients in Norway use one of the NOACs daily, the yearly cost would surpass NOK 500 million per year. In 2011, the turnover for warfarin was in total NOK 77 mill in Norway, regardless of diagnosis.

Economic evaluation - Results

We calculated lifetime costs and effectiveness in terms of QALYs, for all relevant drugs and for different combinations of risk factor levels according to CHA_2DS_2-VASc and HAS-BLED based on simulations of the model (1000 iterations). We also calculated net health benefits based on a suggested threshold cost-effectiveness of NOK 588 000 per QALY. First, results for patients with moderate and high risk of stroke are presented in detail, and then all the risk groups are presented with only main conclusions. Finally, several scenario analyses were conducted to explore robustness of the results.

AF patients with medium risk of stroke

Results for the group with CHA_2DS_2-VASc=1 and HAS-BLED=0 (medium risk of stroke) are presented in Figure 2 and Table 20. All four points below the dotted WTP line in Figure 2 represent alternatives that are expected to be cost-effective compared to warfarin for this risk group.

Figure 2 Mean incremental costs and effects for new oral anticoagulants compared to warfarin (dotted line represents WTP)
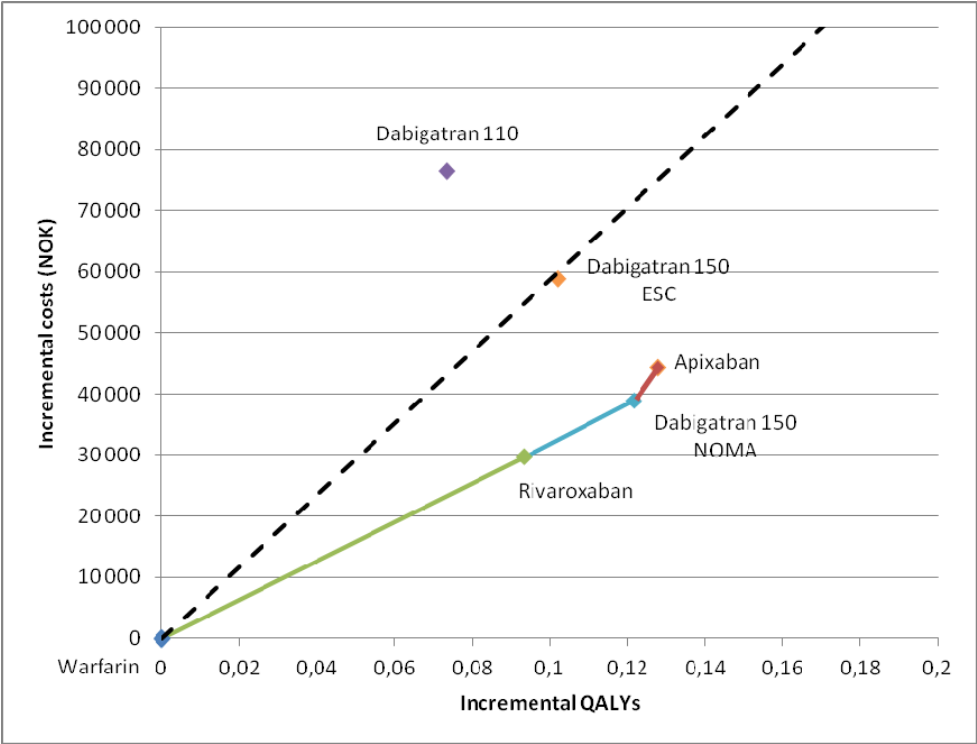
In Figure 2, the incremental cost *vs.* incremental effectiveness is pictured in a traditional way, which shows the strategies along a frontier (green, blue and red line). The line from warfarin to rivaroxaban, dabigatran and finally to apixaban represent the cost-effectiveness frontier, meaning that at different WTP, all four drugs could be considered the most cost-effective. Points not on this frontier are said to be "dominated" by the others. The point farthest from the WTP line is the most cost-effective (dabigatran 150, switching to dabigatran 110 at age 80 (labelled as "Dabigatran 150 NoMA")). The numbers are presented in Table 20 for only the non-dominated strategies (incremental costs and effects are relative to the strategy above, equivalent to the green, blue and red lines of Figure 2).

Expected remaining QALYs for a 65-year old atrial fibrillation patient with medium risk of stroke was estimated to be 13.00 QALYs (discounted: 9.12 QALYs) if treated with warfarin. The discounted incremental QALYs of using rivaroxaban instead are 0.09 and the discounted incremental costs are 29 660, giving an incremental cost-effectiveness ratio of NOK 317 550 per QALY.

The discounted incremental costs and effects of using dabigatran 150 mg (shifting to 110 mg at age 80) compared to rivaroxaban are 9 300 and 0.03, respectively, at an ICER of NOK 328 000 per QALY.

Apixaban is more effective than dabigatran (150 mg), with a discounted incremental QALY of 0.01 per patient. The discounted incremental costs of 5 300 gives an ICER of 882 000, which is above 588 000, meaning that the increased effectiveness of apixaban is not worth the costs according to the assumed WTP. The negative incremental net health benefit indicates that even though apixaban increases effectiveness for this patient group, the increased cost would, in theory, give more health gain elsewhere in the health care system.

Table 20 Lifetime costs and effects (discounted) of new oral anticoagulants and warfarin when CHA_2DS_2-VASc =1 and HAS-BLED=0

STRATEGY	Lifetime costs	Lifetime effects	Incremental cost (NOK)	Incremental effects (QALYs)	ICER	INHB
Warfarin	458 510	9.12				
Rivaroxaban	488 170	9.21	29 660	0.09	317 550	0.04
Dabigatran 150 NoMA	497 467	9.24	9 297	0.03	328 174	0.01
Apixaban	502 789	9.25	5 323	0.01	881 627	-0.003

NOK=Norwegian kroner

QALYs=Quality adjusted life years

ICER=Incremental cost-effectiveness ratio

INHB=Incremental net health benefit

A different way of presenting the results is to rank the strategies according to net health benefit (Table 21). This table shows the ranking of the strategies when taking into consideration the suggested threshold for cost-effectiveness of NOK 588 000 per QALY (14). The rankings indicate that each of the three NOACs give a slight increase in effectiveness compared to warfarin in the given risk group. In Table 21, the INHB represents the distance from the dotted line in Figure 2; the bigger the distance below the line (the bigger INHB), the more cost-effective.

Table 21 Lifetime costs and effects (discounted) of new oral anticoagulants and warfarin when CHA$_2$DS$_2$-VASc =1 and HAS-BLED=0

Interventions	Lifetime costs	Lifetime effects	NHB**	INHB***
Dabigatran 150 NoMA*	497 467	9.24	8.40	0.06
Apixaban	502 789	9.25	8.39	0.05
Rivaroxaban	488 170	9.21	8.38	0.04
Dabigatran 150 ESC*	517 394	9.22	8.34	0.00
Warfarin	458 510	9.12	8.34	
Dabigatran 110	535 027	9.19	8.28	-0.06

*Dabigatran 110 above age 80 in NoMA and above 75 in ESC

**Net health benefit given WTP of NOK 588 000 per QALY

***INHB=Incremental net health benefit compared to warfarin

We ran the model with 1 000 iterations. Results of the simulations are presented as scatter-plots in the cost-effectiveness plane (Figure 3) and as combined cost-effectiveness acceptability curves and cost-effectiveness acceptability frontiers, CEAFs (Figure 4). In Figure 3, each point represents incremental costs and effects of one intervention compared to warfarin from one run of the model. These figures indicate that the three strategies most likely to be cost effective are apixaban (33%), dabigatran 150 mg (36%) and rivaroxaban (29%). However, as can be seen from the table attached to Figure 3, the probability of warfarin being cost-effective compared to each oral anticoagulant separately ranges between 17% and 79%.

Figure 3 Cost-effectiveness scatter-plot compared to warfarin (incremental effectiveness
(QALYs) on x-axis and incremental costs (NOK) on y-axis)
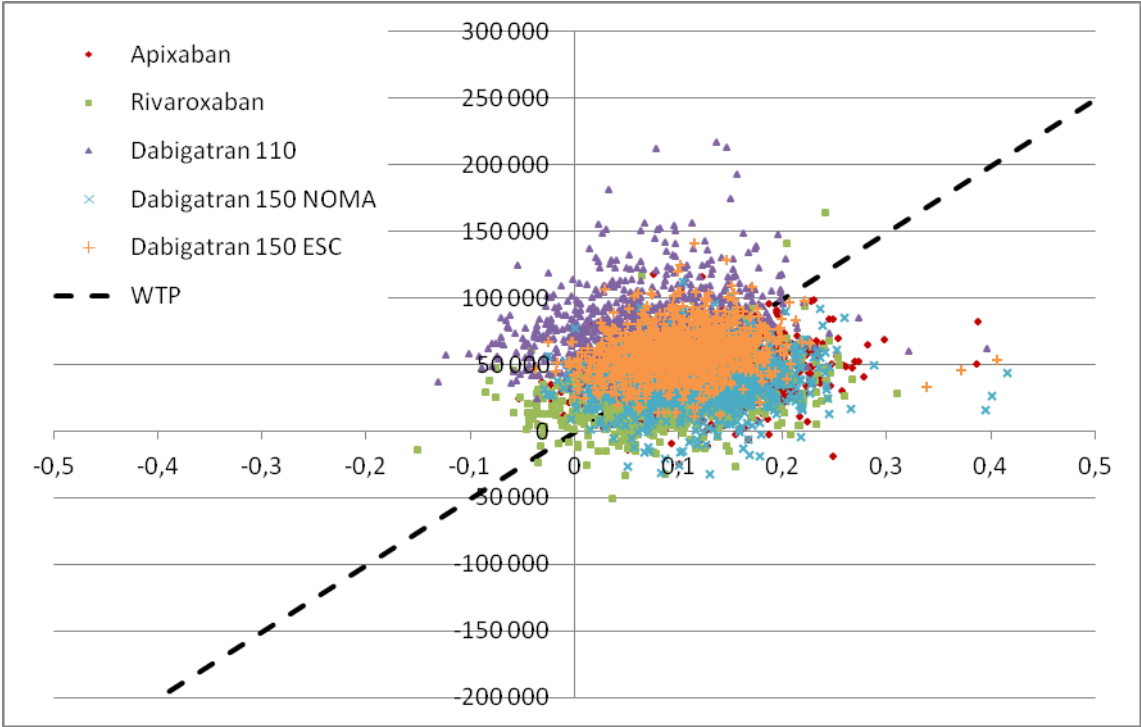
Component	Incr. Eff.	Incr. Cost	ICER	Apixaban	Rivaroxaban	Dabigatran 110	Dabigatran 150 NoMA	Dabigatran 150 ESC
C1	IE>0	IC<0	Dominant	1 %	5 %	0 %	3 %	0 %
C2	IE>0	IC>0	<588 000	82 %	71 %	21 %	80 %	50 %
C3	IE<0	IC<0	>588 000	0 %	0 %	0 %	0 %	0 %
C4	IE>0	IC>0	<588 000	16 %	18 %	67 %	17 %	49 %
C5	IE<0	IC<0	>588 000	0 %	0 %	0 %	0 %	0 %
C6	IE<0	IC>0	Dominated	1 %	6 %	12 %	1 %	1 %
Σ C1-C3	Percentage cost-effective compared to warfarin			83 %	76 %	21 %	82 %	50 %
	Percentage most cost-effective			33 %	29 %	2 %	36 %	0 %

In figure 4, probability of being the most cost-effective alternative is plotted for all
analysed strategies for varying cost-effectiveness threshold. For thresholds below
320 000, warfarin is cost-effective, for thresholds between 320 000 and 340 000,
rivaroxaban is cost-effective, for thresholds between 340 000 and 900 000, dabiga-
tran 150 mg is cost-effective, while apixaban is cost-effective for thresholds above
900 000. Because we have assumed a threshold of 588 000 for Norway, dabigatran
would be cost-effective. The figure illustrates that there is great uncertainty regard-
ing which drug is the most cost-effective, even if the threshold was lower or higher.

Figure 4 Cost-effectiveness acceptability curve (whole lines are CEAF)
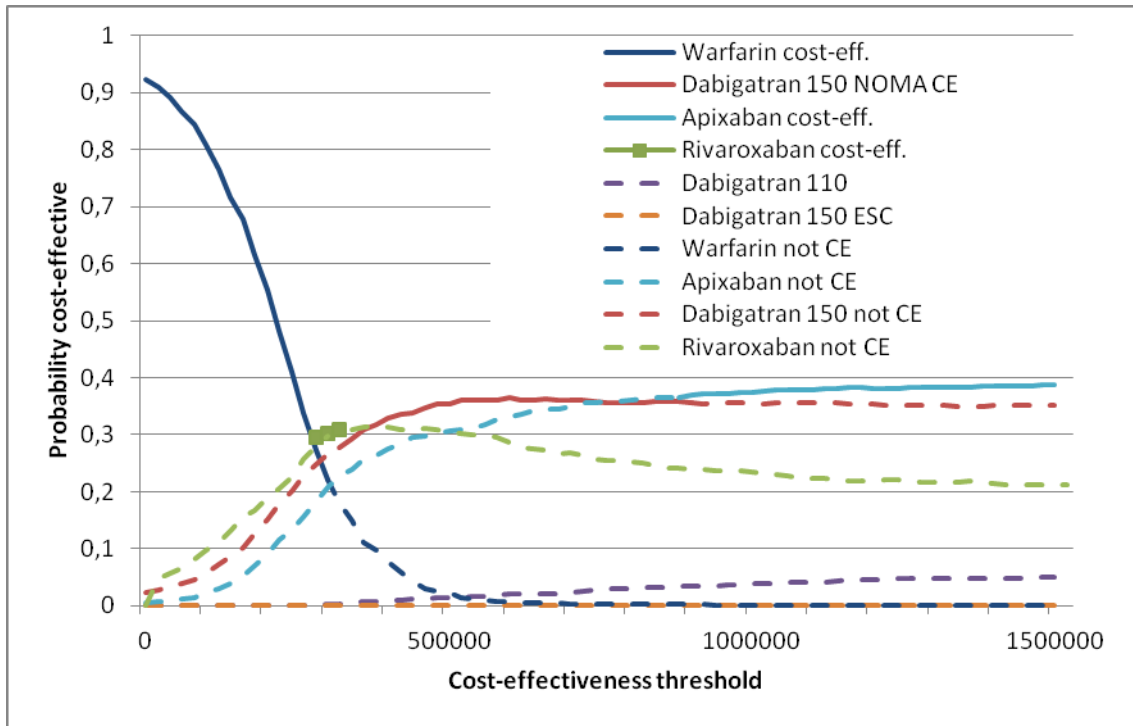
AF patients with high risk of stroke

Results for the group with CHA_2DS_2-VASc=2 and HAS-BLED=1 (high risk of stroke) are presented in Figure 5 and Table 22. All four points below the dotted WTP line in Figure 5 represents alternatives that are expected to be cost-effective compared to warfarin for this risk group. The point farthest from the WTP line is the most cost-effective (dabigatran 150 mg).

Figure 5 Mean incremental costs and effects for new oral anticoagulants compared to warfarin (dotted line represents WTP)
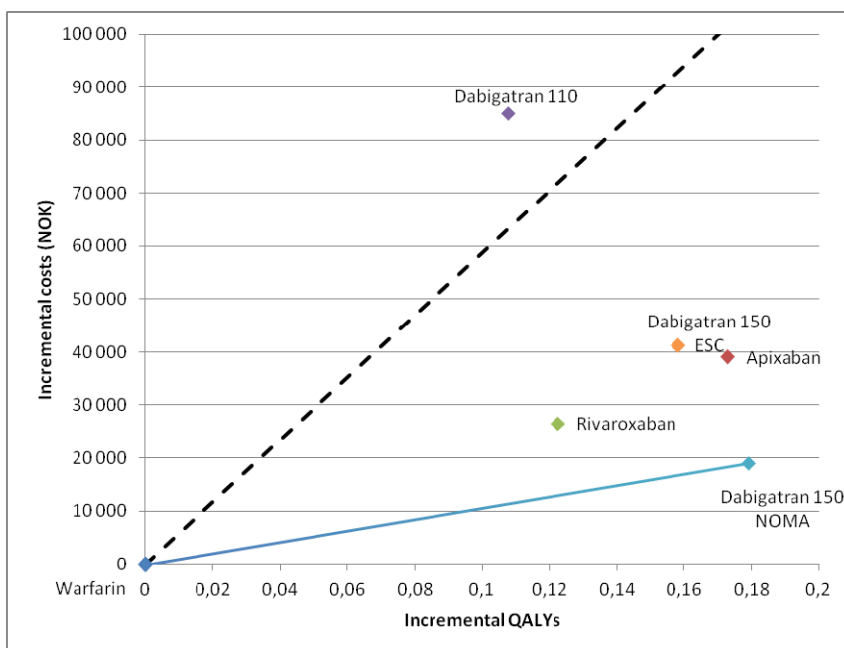
In Figure 5, the incremental cost *vs.* incremental effectiveness is pictured in a traditional way, which shows the strategies along a frontier (blue line). As can be seen from Figure 5, only warfarin and dabigatran 150 mg lie along this frontier, and the rest are "dominated" by these two. The numbers are presented in Table 22 for only the non-dominated strategies. Expected remaining QALYs for a 65-year old atrial fibrillation patient with high risk of stroke was estimated to be 11.44 QALYs (discounted: 8.25 QALYs) if treated with warfarin. The incremental QALY of using dabigatran compared to warfarin is 0.18 QALYs, and the incremental costs are NOK 19 000, giving an incremental cost-effectiveness ratio of NOK 106 000 per QALY.

Table 22 Lifetime costs and effects of new oral anticoagulants and warfarin when CHA_2DS_2-VASc=2 and HAS-BLED=1

STRATEGY	Lifetime costs	Lifetime effects	Incremental cost (NOK)	Incremental effects (QALYs)	ICER	INHB
Warfarin	548 698	8.25				
Dabigatran 150 NoMA	567 702	8.43	19 004	0.18	106 142	0.15

NOK=Norwegian kroner

QALYs=Quality adjusted life years

ICER=Incremental cost-effectiveness ratio

INHB=Incremental net health benefit

Ranking the strategies according to net health benefit (Table 23) show that not only warfarin and dabigatran 150 mg are relevant interventions in the given risk group. This table is based on the tentative threshold for cost-effectiveness of NOK 588 000 per QALY. In Table 23, the INHB represents the horizontal distance from the dotted line in Figure 5; the bigger the distance below the WTP-line (INHB), the more cost-effective. For this risk group, dabigatran 150 mg is both the most effective, and less costly than all other NOACs.

Table 23 Lifetime costs and effects of oral anticoagulants when CHA_2DS_2-VASc=2 and HAS-BLED=1

Interventions	Lifetime costs	Lifetime effects	NHB**	INHB**
Dabigatran 150 NoMA	567 702	8.43	7.46	0.15
Apixaban	587 703	8.42	7.42	0.11
Dabigatran 150 ESC	589 909	8.41	7.41	0.09
Rivaroxaban	575 239	8.37	7.40	0.08
Warfarin	548 698	8.25	7.32	
Dabigatran 110	633 741	8.36	7.28	-0.04

*Dabigatran 110 above age 80 in NoMA and above 75 in ESC

**Net health benefit given WTP of NOK 588 000 per QALY

***Incremental net health benefit is difference between NHB for each intervention and warfarin

Results of the simulations with 1 000 iterations are presented as scatter-plots in the cost-effectiveness plane (Figure 6) and as cost-effectiveness acceptability frontiers (Figure 7). These figures indicate that the three strategies most likely to be cost effective are dabigatran 150 mg (52%), apixaban (28%) and rivaroxaban (18%). As for medium risk patients, the probability of warfarin being cost-effective compared to each oral anticoagulant separately is not negligible, and ranges from 4% to 65%.

Figure 6 Cost-effectiveness scatter-plot compared to warfarin (incremental effectiveness (QALYs) on x-axis and incremental costs (NOK) on y-axis)
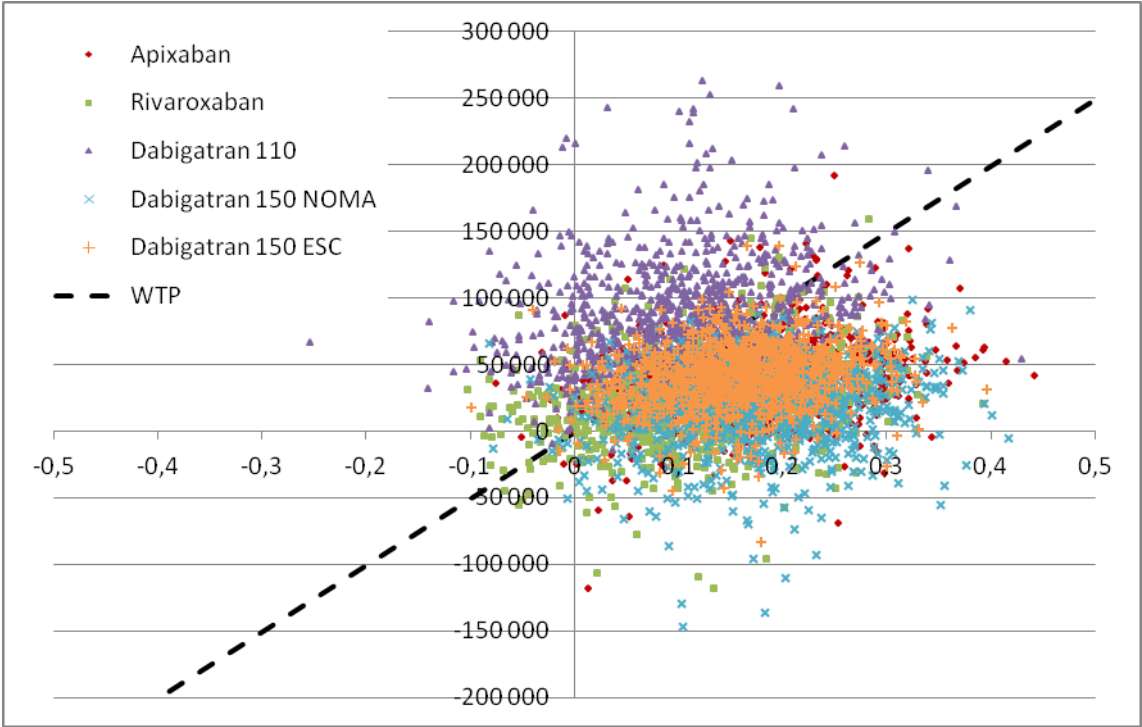
Component	Incr. Eff.	Incr. Cost	ICER	Apixaban	Rivaroxaban	Dabigatran 110	Dabigatran 150 NoMA	Dabigatran 150 ESC
C1	IE>0	IC<0	Dominant	7 %	14 %	0 %	22 %	4 %
C2	IE>0	IC>0	<588 000	84 %	67 %	35 %	74 %	86 %
C3	IE<0	IC<0	>588 000	0 %	1 %	0 %	0 %	0 %
C4	IE>0	IC>0	<588 000	8 %	11 %	55 %	3 %	9 %
C5	IE<0	IC<0	>588 000	0 %	1 %	0 %	0 %	0 %
C6	IE<0	IC>0	Dominated	1 %	5 %	10 %	1 %	1 %
Σ C1-C3	Percentage cost-effective compared to warfarin			91 %	83 %	35 %	96 %	90 %
	Percentage most cost-effective			28 %	18 %	2 %	52 %	0 %

For high risk patients, there is less uncertainty regarding which drug is cost-effective; warfarin is the choice for threshold below 120 000, while dabigatran 150 mg is the choice for all thresholds above. For higher thresholds, apixaban gets more likely to be cost-effective, this is because at higher threshold, the price is less important.

Figure 7 Cost-effectiveness acceptability curves (whole lines are CEAF)
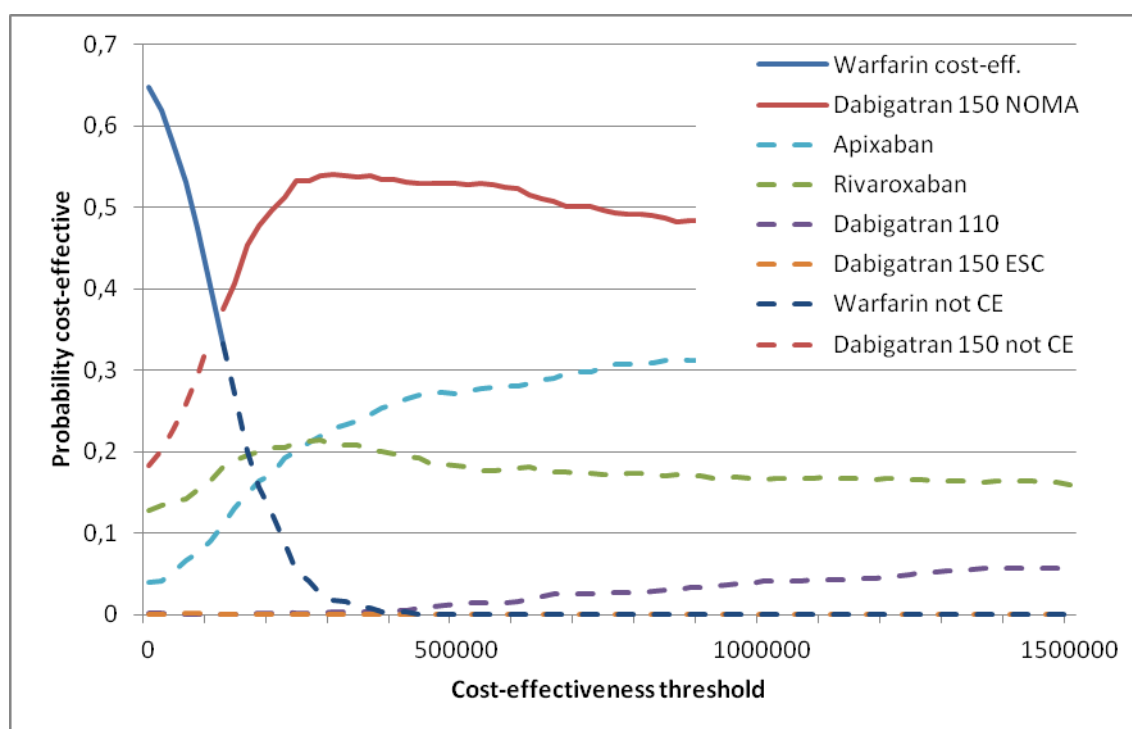
Analyses of different risk groups

In Table 24, we present the results from analyses such as those in Tables 21 and 23, for different combinations of CHA_2DS_2-VASc and HAS-BLED scores. In each of the 30 cells of the table, the most-cost-effective alternative for the given combination of risk factors is shown. The probabilities of being the most cost-effective alternative (at a WTP of 588 000) are given in parentheses, as calculated in Figures 4 and 7. The table shows that apixaban is most cost-effective for CHA2DS2-VASc=1 if HAS-BLED is high (3 or more), and that dabigatran 150 mg is most cost-effective for all other risk groups. Note that it is not necessary to have probability>50% to be cost-effective, because there are six different alternatives (For instance in Figure 4, no alternatives have probability higher than 40%).

Table 24 The most cost-effective alternative for varying CHA_2DS_2-VASc and HAS-BLED scores (percentage most cost-effective in parentheses)

| HAS-BLED | CHA$_2$DS$_2$-VASc | | | | | |
	1	2	3	4	5	6
0	D150 (36%)	D150 (56%)	D150 (58%)	D150 (63%)	D150 (72%)	D150 (70%)
1	D150 (38%)	D150 (52%)	D150 (61%)	D150 (67%)	D150 (70%)	D150 (71%)
2	D150 (39%)	D150 (52%)	D150 (62%)	D150 (68%)	D150 (71%)	D150 (74%)
3	Apix (39%)	D150 (51%)	D150 (60%)	D150 (66%)	D150 (69%)	D150 (74%)
4	Apix (47%)	D150 (53%)	D150 (58%)	D150 (66%)	D150 (71%)	D150 (69%)

Apix = Apixaban 5 mg twice daily

D150 = Dabigatran 150 mg twice daily up to 80 years, thereafter; dabigatran 110 mg (the Dabigatran 150 NoMA alternative)

In risk groups analysed for Table 24, apixaban had the highest expected effectiveness for CHA_2DS_2-VASc=1, while dabigatran 150 mg (switching to 110 mg after age 80) was the most effective in all higher risk groups.

Value of information analyses

Based on the Monte Carlo simulations of the 30 different risk groups (presented in Table 24) we also calculated expected value of perfect information, EVPI (Table 25). This number indicates to what extent conducting new research will be cost-effective. From Table 25, it becomes evident that risk groups where dabigatran 150 mg have high probability of being the most cost-effective, also have lower EVPI (and vice versa). The table indicates that research is more worthwhile the lower the risk of stroke (CHA_2DS_2-VASc).

Table 25 Expected value of perfect information (per patient)

	CHA_2DS_2-VASc					
HAS-BLED	1	2	3	4	5	6
0	24 388	20 324	20 805	17 817	15 142	15 872
1	24 377	21 903	19 208	16 885	16 075	16 000
2	21 295	20 609	17 532	16 419	13 956	12 543
3	22 188	22 895	18 482	17 060	15 095	12 862
4	24 391	20 949	20 209	16 255	13 783	13 782

If new research are to be conducted on any of the 214 uncertain input parameters to our model, it would be useful to see what type of parameters new research could improve the most. We performed expected value of perfect information *on parameters* to explore which of the parameters had the biggest impact on the results, and to indicate the value of more research. We chose to do this analysis on the group with medium risk of stroke (CHA_2DS_2-VASc=1 and HAS-BLED=0). Based on the initial simulations of 1000 iterations, we concluded that the simulations are approximately stable at approximately 250 iterations. Number of iterations in the outer loop does not require as many iterations as the inner loop, hence EVPPI analyses were performed with 50x250 iterations. In the EVPPI analyses, we grouped parameters into 4 groups (efficacy, epidemiology, costs and QALYs). The EVPPI of each of these groups are plotted in Figure 8.

Figure 8 EVPPI per patient for different groups of parameters (CHA$_2$DS$_2$-VASc=1 and HAS-BLED=0)
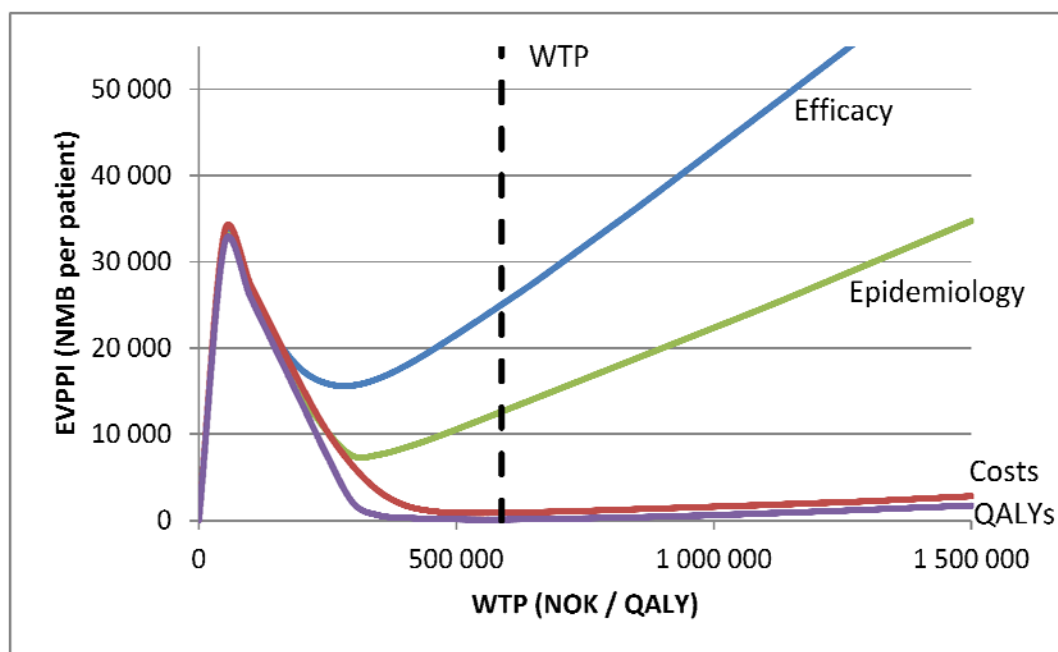
For values of WTP above NOK 200 000 per QALY, efficacy data had the highest EVPPI. At a WTP of NOK 588 000 per QALY, the EVPPI per patient was NOK 25 000 for medium-risk patients.

Scenario analyses

Apixaban is the newest of the three new oral anticoagulants, and its price is at the moment the highest of the three new drugs. Apixaban is also the most effective in some risk groups. In a separate one-way sensitivity analysis for medium risk patients (CHA$_2$DS$_2$-VASc=1 and HAS-BLED=0), we explored at what price apixaban would be the most cost-effective alternative (Figure 9). At a yearly price per patient of maximum NOK 8 913 (NOK 12.20 per pill), which is somewhat lower than today's price, apixaban was the most cost-effective alternative. Likewise, a rivaroxaban price below 7 020 per year (NOK 19.22 per pill) makes it cost-effective compared to the others. This result is due to the fact that apixaban seems to be a bit more efficacious than dabigatran 150 mg (NoMA) for medium risk patients.

Figure 9 One-way sensitivity on price of apixaban, rivaroxaban and warfarin for medium risk patients
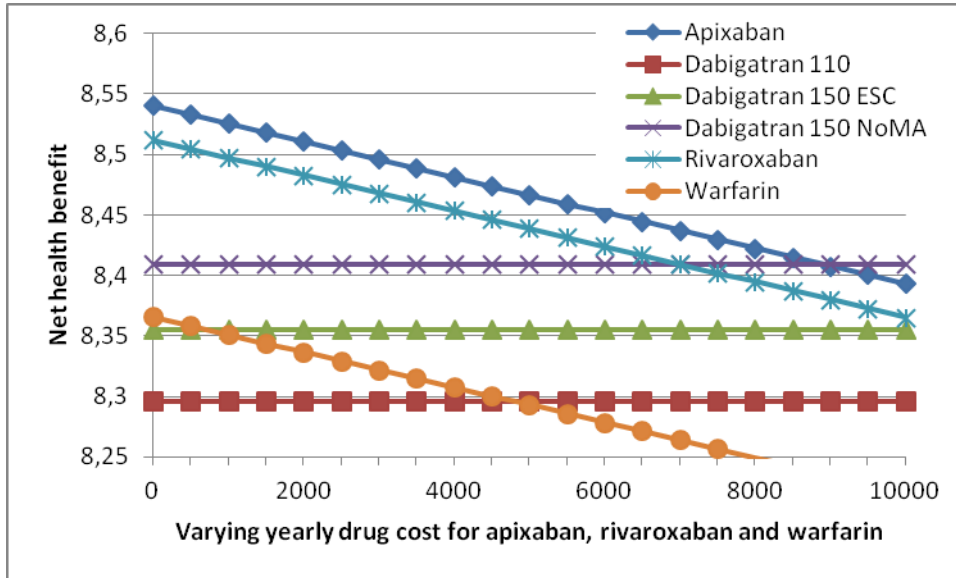
For high risk patients, dabigatran 150 mg (NoMA) was more efficacious compared to the other alternatives. Hence, prices of apixaban and rivaroxaban had to be lower to be cost-effective. When varying prices down towards zero (Figure 10), apixaban had to cost NOK 5 989 per year (8.20 per pill), while rivaroxaban had to cost NOK 2 231 (6.11 per pill) to be the most cost-effective.

Figure 10 One-way sensitivity on price of apixaban, rivaroxaban and warfarin for high risk patients
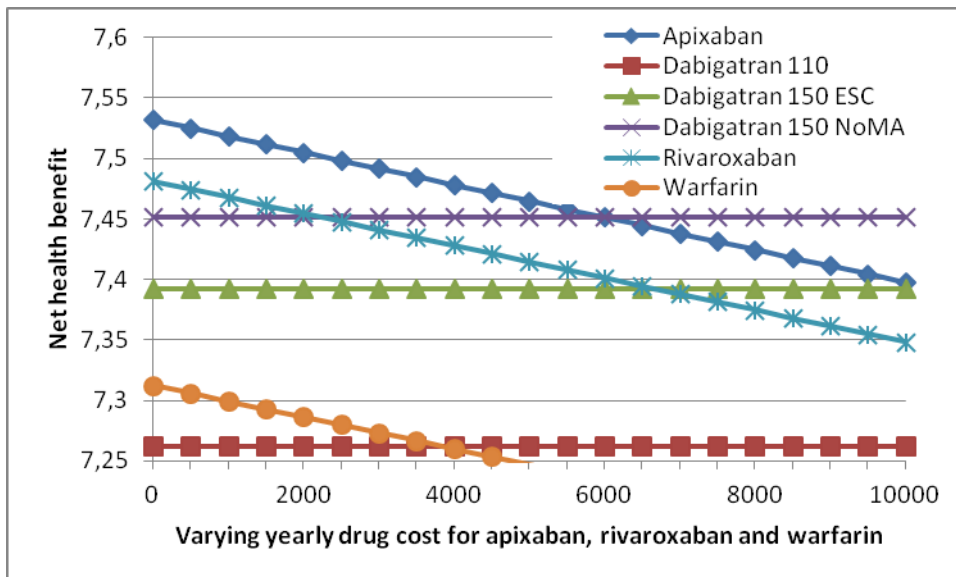
In our base case analyses we assumed lifelong use of the medications. The RCTs of efficacy have, however, only 3 to 4 years of follow-up, and the base case therefore rests on the assumption that the treatment effect can be extrapolated to lifetime. We cannot be certain whether the efficacy reported in these trials will continue for the remainder of the patients' lives. Hence, we performed analyses in which we assumed

only 4 years of treatment effectiveness with new drugs (Table 25 and 26). These analyses indicate somewhat smaller effectiveness of the new drugs compared to warfarin. Due to the smaller effectiveness, drug prices become more influential for the results. For medium risk patients, these assumptions result in rivaroxaban being the most cost-effective alternative.

Table 26 Scenario analysis with only 4 years treatment (medium risk)

All	Lifetime costs	Lifetime effects	NHB*	INHB**
Rivaroxaban	466 906	9.1761	8.3820	0.0053
Apixaban	471 646	9.1840	8.3819	0.0052
Dabigatran 150	471 979	9.182	8.380	0.003
Warfarin	456 793	9.154	8.377	
Dabigatran 110	477 256	9.172	8.360	-0.017

*Net health benefit given WTP of NOK 588 000 per QALY

**Incremental net health benefit compared to warfarin

Table 27 Scenario analysis with only 4 years treatment (high risk)

All	Lifetime costs	Lifetime effects	NHB*	INHB**
Dabigatran 150	555 174	8.298	7.354	0.048
Apixaban	561 650	8.294	7.339	0.033
Rivaroxaban	557 591	8.279	7.331	0.025
Warfarin	549 223	8.240	7.306	
Dabigatran 110	573 682	8.274	7.299	-0.007

*Net health benefit given WTP of NOK 588 000 per QALY

**Incremental net health benefit compared to warfarin

Because the RE-LY trial included patients with a lower risk of stroke than the other trials, we performed a scenario analysis based on efficacy data from subgroup analyses from the RE-LY trial with only on efficacy data from risk groups with CHADS2 score of 2 or higher (20;62). In these analyses the dabigatran alternatives were more efficacious and more cost-effective.

As pointed out in a re-analysis of the RE-LY trial, efficacy of dabigatran compared to warfarin was not the same in all countries. Countries with higher proportions of patients within target INR range had smaller differences between dabigatran and warfarin (44). We performed separate analyses on the subgroup with INR closest to the assumed level in Norway (second best controlled of four groups). These analyses indicated that there were only small differences between the original analyses and this subgroup (data not shown). In the mentioned reanalysis of RE-LY, the quarter of patients who were best controlled was also analysed. For this group, efficacy data indicated less effect of dabigatran compared to warfarin. Even though Norway as a whole is not in this group, we regarded it as relevant to include analyses of cost-effectiveness based on these efficacy data. These analyses indicated that for this

group of well-controlled patients, it is 99% and 94% likely that warfarin is cost-effective compared to NOACs for medium and high risk patients, respectively.

In separate analyses with shorter cycle length (one month), results were similar, except that apixaban was the most cost-effective for medium risk patients. In analyses of 75 year old AF patients, results were similar to results for 65 year old patients, but here apixaban was also the most cost-effective for medium risk patients.

As previously indicated, unlike patients on warfarin, patients on NOACs do not require regular INR measurements. There are however, several uncertainties regarding how frequent the clinical follow up will be for patients who start with NOACs. We considered more closely two of several relevant aspects. First, we explored whether non-adherence could influence the results by assuming a 6% decline in effect of NOACs per quarter of a year. These analyses indicated that the probability of warfarin being the most cost-effective alternative increased from 1% to 72% for medium risk patients and from 0% to 5% for high risk patients.

Discussion

In this HTA we have systematically reviewed and summarized one HTA report of new oral anticoagulants (NOACs) compared with warfarin in patients with atrial fibrillation with regard to efficacy and safety. We have further performed an economic evaluation to examine the cost-effectiveness of these NOACs compared to warfarin in atrial fibrillation patients for different risk groups in a Norwegian setting.

Summary of results

We found one Canadian HTA report with a systematic review of clinical studies. The main efficacy data were three randomized controlled trials comparing each of the new oral anticoagulants with warfarin. All three randomized controlled trials reported statistically significant reduction of intracranial bleeding compared to warfarin. For the outcomes all-cause mortality, ischemic stroke, gastrointestinal bleeding and myocardial infarction, results were inconclusive. Quality of evidence for the outcomes was generally regarded as low or very low.

Modelling results in terms of QALYs indicate that for AF patients with medium risk, apixaban was most effective, while for high risk patients, dabigatran 150 mg was most effective. Regarding cost-effectiveness, the lower price of dabigatran indicated that dabigatran 150 mg could be cost-effective in most risk groups (28 of 30 analysed groups). As can be seen from our probabilistic sensitivity analyses (PSA), these results are highly uncertain, and they rely heavily on the input, where particularly efficacy data are a major factor. In addition to our PSA, we tested several changes of scenario. The scenario with well controlled patients substantially increased the probability of warfarin being cost-effective.

All assessed interventions yielded comparable estimates of health and economic consequences. Which intervention is most cost-effective depends largely on the efficacy estimates upon which the model is based and on the prices of the medications.

Strengths and weaknesses of this report

Our data on efficacy were based on an HTA report from Canada. This report included all clinical trials of NOAC *vs.* warfarin for AF. However, they only used the 3

major studies to estimate efficacy and safety, and new trials may alter the results, if they are performed. Because only one RCT was included per direct comparison and some of the events are rare, the results are uncertain for these comparisons. For the indirect comparisons the results are even more uncertain, not only because there are no direct comparisons, but also because the trials were heterogeneous in design and inclusion criteria.

The model used in this report is relatively comprehensive compared to other models for economic evaluations. The model has 8 different health states and more than 200 different parameters with probability distributions. We believe that most of the uncertainties regarding the decisions in question are incorporated into this model.

The model has limitations and simplifications that make it manageable. The choice of events and health states is always open for discussion. We chose to include the most prevalent and serious events, but more events, health states and combinations of health states could have been included. In this model, we potentially could have included events like minor bleeds and major bleedings other than GI or intracranial. We excluded these conditions because of modeling complexity and heavy data requirements, and because we believe that they are less important for the overall conclusions. But the exact influence of the omitted diagnoses on the results is uncertain.

Data on incidence are based on Swedish and Danish registries. Ideally they should be based on Norwegian data. We identified one small study reporting Norwegian data on intracranial bleeding. This study reported 2 bleedings among 107 atrial fibrillation patients during a total of 215 years of follow-up (average=2 years per patient). This number corresponds well with our data, but the data set was considered too small for the scope of this analysis. Similarly, the same study reported 2 cerebral emboli, which is a bit lower than what was observed in the included data.

As with all new drugs, the issue of potential side effects is not fully explored for the NOACs. Warfarin, however, has been used for more than 50 years in Norway, and there is a lot of evidence regarding adverse effects. In addition, doctors are familiar with its use. There is great uncertainty regarding whether the NOACs will have side effects that were not identified in trials and the monitoring of these new drugs is essential for the safety of patients.

One of the main arguments for using NOACs has been that patients on warfarin have to be regularly monitored for INR level while this is not necessary with the new drugs. Given that monitoring is somewhat better in Norway than in other countries, this argument is potentially less applicable in Norway than in other counties. We have included the costs of the INR tests in our analyses and it appears that warfarin is a cheaper alternative, even with these costs included. There is, however, great uncertainty about the average number of GP visits under current practice, and even more so regarding the number of GP visits that will be necessary with NOACs.

We have not included any QALY loss related to GP visits and INR-control. There may, however, be some loss for patients who regularly have to see their GP.

The new oral anticoagulants will require allocation of funds in the health care budget if these are to be preferred over warfarin. This has already been done to some extent for 2013. On the other hand, it is not clear to what extent reduced use of INR tests will be identifiable in any budget.

In trials, patients with NOACs were followed up similarly to patients on warfarin. Because this follow-up is supposed to be lower in real practice for NOAC patients but not for warfarin patients, one may observe lower compliance in real life. This may in turn affect the overall effectiveness of the drugs.

Patients who receive too much warfarin can be treated with vitamin K as an antidote; The current lack of an antidote for NOACs has been claimed to be a problem, but they also have a shorter half-life. These issues have not been addressed in this report.

The prices of these drugs are expected to fluctuate more than usual, given that three different pharmaceutical companies have three drugs with similar efficacy data. Price changes alter the estimated lifetime costs as well as the cost-effectiveness of using the drugs.

In trials, patients on NOACs have been followed for up to 4.1 years. We model life-long use of the medications and assume life-long drug effectiveness for compliant patients.

QALY-values used in this report are all gathered from studies which have used EQ-5D. This provides consistency both within the report and across different economic evaluations, as this is the most used tool for assessing patients' health-related quality of life. The QALY-values should ideally be based on one study to give increase consistency even further, but this was not available. For some, internal ranking of the QALY values may not seem logical. It is, however, important to point out that these values only represent quality of life during the specified period. Duration of this period, and what happens afterwards (e.g. sequelae or death) is modelled separately. In our EVPPI-analyses, QALYs were not among the groups of parameters with the biggest impact, indicating that uncertainty regarding these parameters affect results to a lower degree than other groups of parameters.

We only included efficacy data published in English. Even though this sometimes may be a limitation, we do not expect that any large randomised controlled trials comparing any of these drugs are published in another language.

Our analyses of different risk groups were restricted to the 30 risk groups with the lowest risk (Table 24). This restriction was due to sparse epidemiological data in the higher risk groups.

We did not have access to patient-level data from any of the included trials. If we had, we could have performed subgroup analyses with efficacy data on several other subgroups. This type of analyses are regularly considered hypothesis-generating, indicating that results would not be intended for priority setting regarding drug use, but rather commissioning of new trials.

Our results compared to other findings/other reviews or results

Several reviews and meta-analyses have examined these four drugs the last year (63-70). The overall message seems to be that we are not yet certain whether warfarin or one of the new drugs is the best option for patients with atrial fibrillation.

While several cost-effectiveness studies have examined these new drugs, to date only the Canadian report has compared all drugs in one analysis, as we have done in this report. The Canadian base case analysis showed a 68% probability that dabigatran 150 mg was the most cost-effective for an average AF patient and a 29% probability for apixaban. Potentially comparable results in our analyses were for the group CHA_2DS_2-VASc=2 and HAS-BLED=1, which are comparable to the Canadian population. The corresponding figures in our model were 52% and 28%, respectively.

Conclusion

There is great uncertainty about which of the oral anticoagulants is most effective, safe and cost-effective for which risk groups. A randomized controlled trial comparing these four drugs head-to-head would add to the evidence base and reduce decision uncertainty.

Implications for practice

There is uncertainty about whether new AF patients would gain by using these new pharmaceuticals, but our analyses indicate that it is possible.

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Appendix

Appendix 1 – literature search

Overview

Databases: Ovid MEDLINE (In-Process & Other Non-Indexed Citations and Ovid MEDLINE
             1946 to Present), Embase (Ovid, 1980 to 2012 Week 11)
             Cochrane Library; Database of Systematic Reviews; CENTRAL (Register of Con-
             trolled Trials),
             CRD (Centre for Reviews and Dissemination); DARE (Database of Abstracts of
             Reviews of Effects), HTA (Health Technology Assessment)
             ISI Web of knowledge, PubMed, HTA organisations (in detail below), Google
             Scholar
Date of Search: 2012.03.19-22
Study Types: Systematic reviews (SR)
             Randomised controlled trials (RCT)
Result: SR: 105 references
             RCT: 29 references (2011-2012 week 12)
             Tot.: 134
Limits**:**   None
Search by: Ingrid Harboe

Syntax guide

/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Truncation symbol, or wildcard: retrieves plural or variations of a word
*sh	Indicates that the marked subject heading is a primary topic
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.tw	Search for text word in title and abstract
.mp	Search the text word in all fields [title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]. Sometimes used for drugs (brand names)
.pt	Publication Type
.rn	CAS registry number

Ovid Medline, Embase search strategy:

Date: 2012-03-19

Result: 16 SR, 31 RCT
Comment: Federated search

1   heart atrium fibrillation/ use emez

2   heart atrium flutter/ use emez

3   atrial fibrillation/ use prmz

4   atrial Flutter/ use prmz

5   ((atri* or auri*) adj3 (fibril?at* or flutter*)).tw.

6   or/1-5

7   dabigatran/

8   dabigatran etexilate/

9   (dabigatran or pradaxa or pradax or prazaxa).mp.

10 rivaroxaban/

11 (rivaroxaban or xarelto).mp.

12 (BAY 59 7939 or BAY 597939 or BAY597939).mp.

13 apixaban/

14 (apixaban or eliquis).mp.

15 bms 562247.mp.

16 or/7-15

17 warfarin/

18 warfarin.mp.

19 or/17-18

20 6 and 16 and 19

21 limit 20 to ("therapy (maximizes specificity)" and "yr= 2011 -current")

22 20 and systematic* review*.ti,ab,kw.

23 limit 20 to "reviews (maximizes specificity)"

24 22 or 23

25 21 or 24

26 remove duplicates from 21

27 remove duplicates from 24

28 26 or 27

Cochrane Library search strategy:
Date: 2012-03-19
Results: **Cochrane Reviews 1**, Technology Assessments 0, Trials 9 (2011-2012)

#1   MeSH descriptor Atrial Fibrillation, this term only

#2   MeSH descriptor Atrial Flutter, this term only

#3   ((atri* or auri*) near/3 (fibril?at* or flutter*)):ti,ab,kw

#4   (#1 OR #2 OR #3)

#5   (dabigatran or pradaxa or pradax or prazaxa or EC3-4-21-5):ti,ab,kw

#6   (rivaroxaban or xarelto):ti,ab,kw

#7   (BAY 59 7939 or BAY 597939 or BAY597939):ti,ab,kw

#8   (apixaban or eliquis):ti,ab,kw

#9   (bms 562247):ti,ab,kw

#10 (#5 OR #6 OR #7 OR #8 OR #9)

#11 (#4 AND #10)

#12 MeSH descriptor Warfarin, this term only

#13 warfarin:ti,ab,kw

#14 (#12 OR #13)

#15 (#4 AND #10 AND #14)

#16 (#15), from 2011 to 2012

CRD search strategy
Date: 2012-03-20
Result: 2
1   MeSH DESCRIPTOR Atrial Fibrillation IN DARE,HTA
2   MeSH DESCRIPTOR Atrial Flutter IN DARE,HTA
3   (atri* fibrillation*) OR (atri* flutter*) OR (auri* fibrillation*) OR (auri* flutter*) IN DARE, HTA
4   #1 OR #2 OR #3
5   (dabigatran or pradaxa or pradax or prazaxa) IN DARE, HTA
6   (rivaroxaban or xarelto) IN DARE, HTA
7   (BAY 59 7939 or BAY 597939 or BAY597939) IN DARE, HTA
8   (apixaban or eliquis) IN DARE, HTA
9   (bms 562247) IN DARE, HTA
10   (EC3-4-21-5) IN DARE, HTA
11   #5 OR #6 OR #7 OR #8 OR #9 OR #10
12   MeSH DESCRIPTOR Warfarin IN DARE,HTA
13   (warfarin) IN DARE, HTA
14   #12 OR #13
15   #4 AND #11 AND #14

Web of Science
Date: 2013-03-20
Result: 66

Topic=(atri* fibrillation or atri* flutter or auri* fibrillation or auri* flutter) AND
Topic=(dabigatran or rivaroxaban or apixaban) AND Topic=(warfarin) AND Document
Types=(Review)
Databases=SCI-EXPANDED Timespan=All Years
Lemmatization=On

HTA-sider:
PubMed search strategy
Date: 2012-03-21
Result: 16 reviews
Limit: published in the last 2 years

#6 Search ((#5) AND #3) AND #4 Limits: Randomized Controlled Trial, Review, published

70

in the last 2 years

#5 Search (#1) OR #2

#4 Search (warfarin[Title/Abstract]) OR "warfarin"[MeSH Major Topic]

#3 Search ((dabigatran[Title/Abstract]) OR rivaroxaban[Title/Abstract]) OR apixa-ban[Title/Abstract]

#2 Search (atrial fibrillation[Title/Abstract]) OR atrial flutter[Title/Abstract]

#1 Search ("atrial fibrillation"[MeSH Major Topic]) OR "atrial flutter"[MeSH Major Topic]

HTA organisations:
Search date: 2012-03-21
Search: dabigatran or rivaroxaban or apixaban
AHRQ, AHTA, AETMIS, FDA, Finohta, IQWIC, KCE, NICE, Sundhedsstyrelsen
Result: no references

CADTH
Result: 1

SBU
Kategori: Hjärt-kåarlsjukdomar
Result: 1

INAHTA
Result: 1

Google scholar
Date: 2012-03-21
Search: "atrial flutter" warfarin dabigatran "systematic review"
Result: 5

Appendix 2 – Articles evaluated for inclusion

	Identified literature	Inclusion or reason for exclusion
1	Therapeutic Review. Safety, Effectiveness, and Cost- Effectiveness of New Oral Anticoagulants Compared with Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation. April 9, 2012. Canadian Collaborative for Drug Safety, Effectiveness and Network Meta – Analysis in collaboration with the Canadian Agency for Drugs and Technologies in Health (CADTH). http://www.cadth.ca/media/pdf/NOAC_Therapeutic_Review_final_report.pdf	Include
2	CHEST. ACCP guidelines http://chestjournal.chestpubs.org/content/141/2_suppl	HTA from CADTH better reporting/more comprehensive
3	Bovio JA, Smith SM, Gums JG. Dabigatran etexilate: a novel oral thrombin inhibitor for thromboembolic disease. Ann Pharmacother 2011 May;45(5):603-14.	Not fulfilling all criteria of a SR
4	Coleman CI, Sobieraj DM, Winkler S, Cutting P, Mediouni M, Alikhanov S, et	HTA from CADTH bet-

	Identified literature	Inclusion or reason for exclusion
	al. Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation. Int J Clin Pract 2012;66(1):53-63.	ter reporting/more comprehensive
5	Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, et al. Risk ofbleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123(21):2363-72.	Study included in HTA from CADTH Possibly include if necessary for subgroup analysis
6	Ezekowitz J, Dorian P, Granger C, Alexander J, Lopes R, Hanna M, et al. Efficacy and safety of apixaban compared to warfarin for prevention of stroke and systemic embolism in 18,201 patients with atrial fibrillation: Primary results of the aristotle trial. Can J Cardiol 2011;Conference(var.pagings):S334-October.	Study included in HTA from CADTH
7	Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J 2011;32(19):2387-94.	Not our predefined subgroup
8	Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine 2011;365(11):981-92.	Study included in HTA from CADTH
9	Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:7S-47S.	Summary of guideline from ACCP
10	Hacke W, Hankey G. Rivaroxaban versus warfarin in patients with AF and prior cerebrovascular disease: Results from the rocket-AF trial. Cerebrovasc Dis 2011;Conference(var.pagings):17.	Study included in HTA from CADTH Subgroup, but no results described
11	Hohnloser SH, Oldgren J, Yang S, Wallentin L, Ezekowitz M, Reilly P, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized evaluation of long-term anticoagulation therapy) trial. Circulation 2012;125(5):669-76.	Study included in HTA from CADTH Re-analysis
12	Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study-. Circulation journal : official journal of the Japanese Circulation Society 2011;75(8):1852-9.	Study included in HTA from CADTH
13	Oldgren J, Alings M, Darius H, Diener HC, Eikelboom J, Ezekowitz MD, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. Ann Intern Med 2011;155(10):660-7, W204.	Study included in HTA from CADTH Possibly include if necessary for subgroup analysis
14	Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Ri-	Study included in HTA

	Identified literature	Inclusion or reason for exclusion from CADTH
	varoxaban versus warfarin in nonvalvular atrial fibrillation. The New England journal of medicine 2011;365(10):883-91.	from CADTH
15	Piccini JP, Patel MR, Mahaffey KW, Fox KAA, Califf RM. Rivaroxaban, an oral direct factor Xa inhibitor. Expert Opinion on Investigational Drugs 2008 Jun;17(6):925-37.	Not fulfilling all criteria of a SR
16	Roskell NS, Lip GYH, Noack H, Clemens A, Plumb JM. Treatments for stroke prevention in atrial fibrillation: A network meta-analysis and indirect comparisons versus dabigatran etexilate. Thromb Haemost 2010;104(6):1106-15.	HTA from CADTH better reporting/more comprehensive
17	SBU. Dabigatran för att förebygga stroke vid förmaksflimmer. SBU Alert-rapport 2011;(4).	Based on subgroups. Full study included in HTA from CADTH
18	Singer DE, Hellkamp AS, Halperin JL, Mahaffey KW, Becker RC, Breithardt G, et al. Individual and regional determinants of time in therapeutic range among patients randomized to warfarin in the rocket af trial of rivaroxaban. Circulation 2011;Conference(var.pagings).	No results presented
19	Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med 2012;doi.	Studies included in HTA from CADTH
20	Uchino K, Hernandez AV. Dabigatran is associated with higher risk of myocardial infarction or acute coronary syndromes: A meta-analysis of non-inferiority randomized controlled trials. Circulation 2011;Conference(var.pagings).	As above. Studies included in HTA from CADTH

Appendix 3 – GRADE assessments

Dabigatran 110 mg vs. warfarin

Authors: TR, TOW. 2012-12-04. Based on HTA report and Dabigatran versus warfarin in patients with atrial fibrillation, Connolly et al.,NEMJ,2009.

Author(s):
Date: 2012-11-27
Question: Should dabigatran 110 mg vs warfarin be used in patients with atrial fibrillation?
Settings:
Bibliography:

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dabigatran 110 mg	Warfarin	Relative (95% CI)	Absolute	Quality	Importance
Quality assessment							**No of patients**		**Effect**			
overall mortaltity (follow-up median 2 years)												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	-	- 0%	HR 0.91 (0.8 to 1.03)	- -	⊕⊕OO LOW	
ischemic stroke or systemic embolism (assessed with: "ischemic or unspecified" stroke)												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3,4]	none	159/6015 (2.6%)	142/6022 (2.4%) 0%	HR 1.11 (0.89 to 1.4)	3 more per 1000 (from 3 fewer to 9 more) -	⊕OOO VERY LOW	
intracranial bleeding												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	-	- 0%	HR 0.31 (0.2 to 0.47)	- -	⊕⊕OO LOW	
acute myocardial infarction												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	-	- 0%	HR 1.35 (0.98 to 1.87)	- -	⊕OOO VERY LOW	
major gastrointestinal bleeding												
1	randomised trials	serious[3]	serious[2]	no serious indirectness	no serious imprecision	none	-	- 0%	HR 1.10 (0.86 to 1.41)	- -	⊕⊕OO LOW	
major bleeding, not gastrointestinal or intracranial - not measured												
0	-	-	-	-	-	none	-	- 0%	-	- -		
quality of life - not measured												
0	-	-	-	-	-	none	-	- 0%	-	- -		

[1] Risk of bias extracted from included SR. Reported as unclear risk of bias for items: adequate sequence generation, allocation concealtment, incomplete outcomes data addressed- efficacy, and incomplete outcomes data addressed-safety. Reported high risk of bias for items: blinding of subjective outcomes assessment and other risk of bias (funding source). Low risk of bias for items: blinidng of objective outcomes assessment and selective reporting. Overall choose to downgrade 1.

[2] One study. Unclear reproducibility.

[3] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm. GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.

[4] Estimate reported at RR in original publication, but methods section describe using Cox-regression. Hence, we report it as HR.

Dabigatran 150 mg vs. warfarin

Authors: TR, TOW. 2012-12-04. Based on HTA report and Dabigatran versus warfarin in patients with atrial fibrillation, Connolly et al.,NEMJ,2009.

Author(s):
Date: 2012-11-27
Question: Should dabigatran 150 mg vs warfarin be used in patients with atrial fibrillatin?
Settings:
Bibliography:

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dabigatran 150 mg	Warfarin	Relative (95% CI)	Absolute	Quality	Importance
Quality assessment							**No of patients**		**Effect**			
overall mortality (follow-up median 2 years)												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	-	- 0%	HR 0.88 (0.77 to 1)	- -	⊕⊕OO LOW	
ischemic stroke or systemic embolism (assessed with: "ischemic or uncertain" stroke)												
1	randomised trials	serious[3]	serious[3]	no serious indirectness	no serious imprecision[3]	none	111/6076 (1.8%)	142/6022 (2.4%) 0%	HR 0.76 (0.6 to 0.98)	6 fewer per 1000 (from 0 fewer to 9 fewer) -	⊕⊕OO LOW	
intracranial bleeding												
1	randomised trials	serious[3]	serious[3]	no serious indirectness	no serious imprecision	none	-	- 0%	HR 0.40 (0.27 to 0.6)	- -	⊕⊕OO LOW	
acute myocardial infarction												
1	randomised trials	serious[3]	serious[3]	no serious indirectness	serious[4]	none	-	- 0%	HR 1.38 (1 to 1.91)	- -	⊕OOO VERY LOW	
major gastrointestinal bleeding												
1	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[3]	none	-	- 0%	HR 1.50 (1.19 to 1.89)	- -	⊕OOO VERY LOW	
major bleeding, not gastrointestinal or intracranial - not measured												
0	-	-	-	-	-	none	-	-	-	-		
quality of life - not measured												
0	-	-	-	-	-	none	-	-	-	-		

[1] Risk of bias extracted from included SR. Reported as unclear risk of bias for items: adequate sequence generation, allocation concealtment, incomplete outcomes data addressed- efficacy, and incomplete outcomes data addressed-safety. Reported high risk of bias for items: blinding of subjective outcomes assessment and other risk of bias (funding source). Low risk of bias for items: blinidng of objective outcomes assessment and selective reporting. Overall choose to downgrade 1.

[2] One study. Unclear reproducibility.

[3] Estimate reported at RR in original publication, but methods section describe using Cox-regression. Hence, we report it as HR.

[4] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm. GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.

Rivaroxaban vs warfarin

Authors: TR, TOW. 2012-12-04. Based on HTA report and Rivaroxaban versus warfarin in nonvalvular atrial fibrillation, Patel et al,. NEMJ 2011

Author(s):
Date: 2012-11-27
Question: Should rivaroxaban vs wararin be used in patienst with atrial fibrillation?
Settings:
Bibliography:

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rivaroxaban	Wararin	Relative (95% CI)	Absolute	Quality	Importance
							No of patients		Effect			
overall mortaltity (follow-up median 1.9 years)												
1	randomised trials	serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	-	-	HR 0.92 (0.82 to 1.04)	-	⊖○○○ VERY LOW	
								0%		-		
intracranial bleeding												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	-	-	HR 0.67 (0.47 to 0.93)	-	⊖○○○ VERY LOW	
								0%		-		
ischemic stroke or systemic embolism												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3,4]	none	149/7061 (2.1%)	161/7082 (2.3%)	HR 0.94 (0.75 to 1.17)	1 fewer per 1000 (from 6 fewer to 4 more)	⊖○○○ VERY LOW	
								0%		-		
acute myocardial infarction												
1	randomised trials	serious[3]	serious[2]	no serious indirectness	serious[3]	none	-	-	HR 0.81 (0.63 to 1.06)	-	⊖○○○ VERY LOW	
								0%		-		
major gastrointestianal bleeding												
1	randomised trials	serious	serious[2]	no serious indirectness	no serious imprecision	none	-	0%	HR 1.60 (1.29 to 1.98)	-	⊖⊖○○ LOW	
major bleeding, not gastrointestinal or intracranial - not measured												
1	-	-[1]	-[2]	-	-	none	-	-	-	-	⊖⊖○○ LOW	
								0%		-		
quality of life - not measured												
0	-	-	-	-	-	none	-	-	-	-		
								0%		-		

[1] Risk of bias extracted from included SR. Reported unclear risk of bias for items: allocation concealtment. Reported high risk of bias for items: incomplete outcomes data addressed- efficacy, incomplete outcomes data addressed-safety and other risk of bias (funding source). Low risk of bias for items: adequate sequence generation, blinding of objective outcomes assessment, blinding of subjective outcomes assessment and selective reporting. Overall choose to downgrade 1.

[2] One study, Unclear reproducability.

[3] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm. GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.

[4] Estimate retrieved from original publication. Data reported as safety on treatment population.

Apixaban vs warfarin

Authors: TR, TOW. 2012-12-04. Based on HTA report and Apixaban versus warfain in patients with artial fibrillation, Granger et al., NEMJ 2011.

No of studies	Design	Quality assessment					No of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Apixaban	Warfarin	Relative (95% CI)	Absolute		
overall mortality (follow-up median 1.8 years)												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	-	-	HR 0.89 (0.8 to 1)	-	⊕⊕OO LOW	
								0%		-		
iscehmic stroke or systemic embolism (assessed with: "ischemic or uncertain "stroke)												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3,4]	none	162/9120 (1.8%)	175/9081 (1.9%)	HR 0.92 (0.74 to 1.13)	2 fewer per 1000 (from 5 fewer to 2 more)	⊕OOO VERY LOW	
								0%		-		
intracranial bleeding												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	-	-	HR 0.43 (0.3 to 0.58)	-	⊕⊕OO LOW	
								0%		-		
acute myocardial infarction												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	-	-	HR 0.88 (0.66 to 1.17)	-	⊕OOO VERY LOW	
								0%		-		
major gastrointestinal bleeding												
1	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	-	-	HR 0.89 (0.7 to 1.14)	-	⊕OOO VERY LOW	
								0%		-		
major bleeding, not gastrointestinal or intracranial - not measured												
0	-	-	-	-	-	none	-	-	-	-		
								0%		-		
quality of life - not measured												
0	-	-	-	-	-	none	-	-	-	-		
								0%		-		

[1] Risk of bias extracted from included SR. Reported unclear risk of bias for items: adequate sequence generation and allocation concealtment. Reported high risk of bias for items: incomplete outcomes data addressed- efficacy, incomplete outcomes data addressed-safety and other risk of bias (funding source). Low risk of bias for items: blinding of objective outcomes assessment, blinding of subjective outcomes assessment and selective reporting. Overall choose to downgrade 1.

[2] One study, Unclear reproducability.

[3] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both 1) no effect and 2) appreciable benefit or appreciable harm. GRADE suggests that the threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%.

[4] Data retrieved from original publication.

Appendix 4 - Mortality

Mortality from statistics Norway (SSB.no) 2011

Age	Both sexes	Age	Both sexes	Age	Both sexes
0	0.002325	36	0.00078	71	0.017296
1	0.000223	37	0.00069	72	0.018568
2	0.000064	38	0.000537	73	0.022165
3	0.000129	39	0.000969	74	0.022865
4	0.000131	40	0.000917	75	0.027413
5	0.000115	41	0.001057	76	0.029477
6	0.00005	42	0.000888	77	0.033646
7	0.00005	43	0.00124	78	0.036517
8	0.000135	44	0.001052	79	0.043882
9	0.00000	45	0.001544	80	0.047461
10	0.000098	46	0.001649	81	0.054239
11	0.000128	47	0.001853	82	0.060125
12	0.000048	48	0.001972	83	0.066792
13	0.000159	49	0.002283	84	0.079613
14	0.000109	50	0.002223	85	0.086091
15	0.000231	51	0.002662	86	0.101718
16	0.00031	52	0.002625	87	0.11036
17	0.000559	53	0.003023	88	0.119123
18	0.000771	54	0.003448	89	0.1383
19	0.000486	55	0.004012	90	0.153166
20	0.000496	56	0.004156	91	0.176645
21	0.000709	57	0.005118	92	0.189565
22	0.000566	58	0.005005	93	0.207787
23	0.000454	59	0.00562	94	0.227718
24	0.000414	60	0.006199	95	0.253637
25	0.000478	61	0.00646	96	0.284632
26	0.000462	62	0.007624	97	0.286833
27	0.000553	63	0.007736	98	0.285681
28	0.000622	64	0.008727	99	0.298067
29	0.000573	65	0.009552	100	0.383089
30	0.000633	66	0.010852	101	0.354474
31	0.000737	67	0.012473	102	0.400893
32	0.000786	68	0.01229	103	0.3564
33	0.000655	69	0.01471	104	0.556478
34	0.000667	70	0.014415	105	0.31857
35	0.000796				