Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium

IMI Work Package 5: Report 2:b:iii Benefit - Risk

Wave 2 Case Study Report: Warfarin

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On behalf of PROTECT Work Package 5 participants

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10 June 2013	Christine Hallgreen	Corrected missing cross-reference link and reference list
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Abbreviations

CPRD	Clinical Practice Research Datalink
HES	Hospital Episodes Statistics
RCT	Randomised clinical trial
TIA	Transient ischaemic attack
AF	Atrial Fibrillation
CI	Cumulative Incidence
RR	Relative Rate
AFASAK	
BAATAF	Boston Area Anticoagulation Trial for Atrial Fibrillation
CAFA	Canadian Atrial Fibrillation Anticoagulation
SPIN I	Stroke Prevention in Atrial Fibrillation
SPINAF	Stroke Prevention in Nonrheumatic Atrial Fibrillation
EAFT	European Atrial Fibrillation Trial

1 Introduction

1.1 Atrial fibrillation disease background

Atrial fibrillation has a prevalence ranging from 0.1% in those under 55 years of age, 3.8% in those over the age of 60, and 9.0% in those over the age of 80 years (1). Patients with atrial fibrillation often have blood clot formation within the heart atrium, due to abnormal blood flow through the heart. These blood clots can produce emboli resulting in ischaemic stroke, which are often associated with death or severe disability (2, 3). It is estimated that the incidence of ischaemic stroke in patients with atrial fibrillation is 3–5% per year, rising to 12–15% in patients with additional risk factors for stroke, including hypertension, diabetes, recent onset cardiac failure, or a prior transient ischaemic attack (TIA) (4).

In patients who have experienced an ischaemic stroke, 15% to 25% have atrial fibrillation (5). Those with untreated atrial fibrillation who have experienced a prior stroke are at considerable risk of additional ischemic strokes, with an average recurrent stroke rate of 13% per year (6).

1.2 Available treatment options

Prevention of stroke (primary prevention) or prevention of a recurrent stroke (secondary prevention), in patients with atrial fibrillation is through the use of drugs, such as anticoagulants, that interfere with the ability of the blood to produce a clot. The principle being that disruption of the clotting pathways will lead to a delay, or reduction in clot formation within the atria of the heart, thereby preventing cerebral emboli. Reducing the ability of the blood to clot however carries a risk of bleeding, including cerebral haemorrhage. Anti-platelet drugs, such as aspirin, have been historically used, but have been shown to be of less value than anticoagulants (7).

Warfarin is the most common anticoagulant currently used to prevent stroke in patients with atrial fibrillation. Warfarin was originally approved for this indication over 50 years ago. The active substance (dicoumarol) was first identified in farm animals which had eaten Sweet-Clover contaminated hay, and then experienced fatal haemorrhages. To this day, warfarin is still used as a rat poison.

Warfarin affects blood coagulation by inhibiting the enzyme ‘vitamin K epoxide reductase’, which results in a reduction of several blood coagulation proteins, particularly prothrombin and factor VII, leading to a prolongation in the production of a thrombin clot (figure 1). As there is a dose response on the enzyme inhibition, larger doses of warfarin will lead to a greater reduction in Vitamin K dependent coagulation proteins, and a greater prolongation in the production of a thrombin clot. Unfortunately because there are many factors that influence the effect of warfarin, including other medications, herbal supplements, diet, physical health, age and individual variations in liver metabolism, the daily dose of warfarin has to be determined by an individual’s response. In addition, once a daily dose is determined, this will need to be continually monitored, as the dose may need to be increased or decreased over time. This monitoring requires regular interactions between patients and health care professional and regular blood tests. Some patients have more consistent dosing requirements than others.

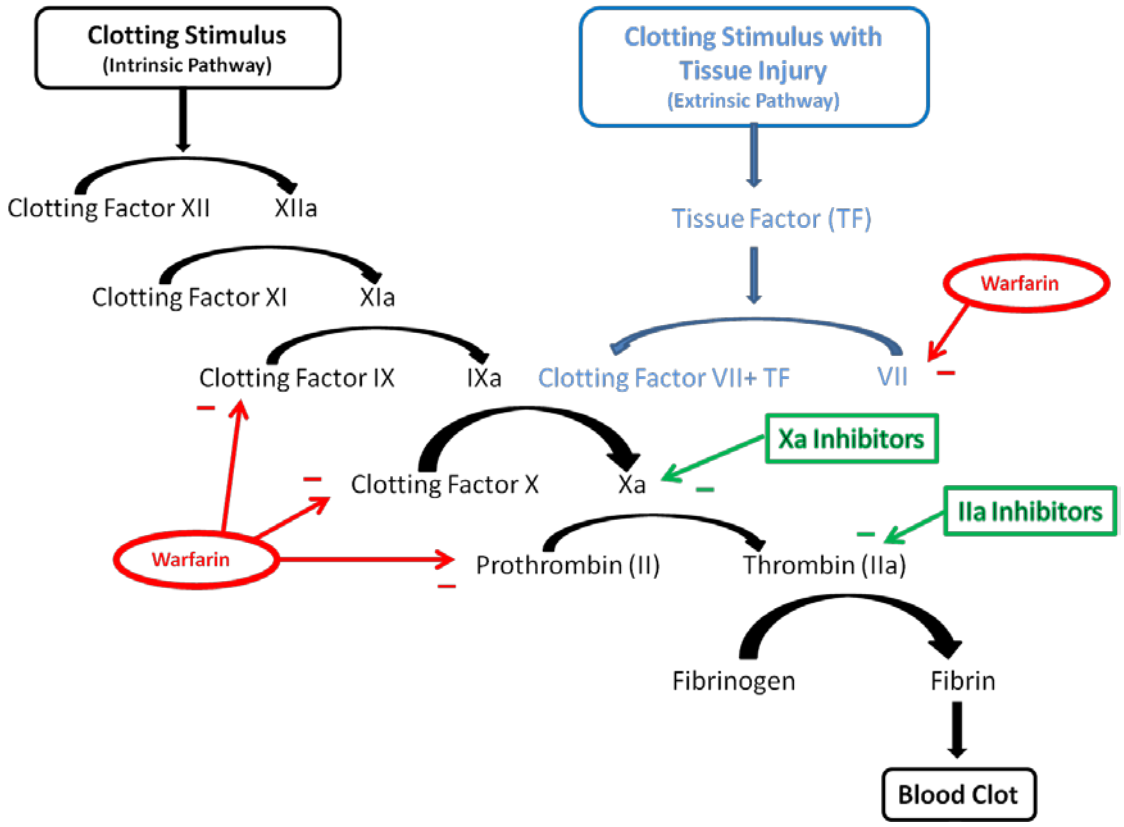


Figure 1: Schematic overview of the mechanism of warfarin's anticoagulation effect

Therapeutic guidelines recommend that patients with atrial fibrillation on warfarin have an INR (International Normalised Ratio) kept between 2-3 (7, 8). This effectively means that the patient's blood will take 2-3 times longer to form a thrombin clot. Patients with atrial fibrillation with an INR less than 2 are still at risk of ischemic stroke, whereas the risk of bleeding increases as the INR increases (9). The most significant of these bleeds are intracranial haemorrhages, of which the majority (70%) are intracerebral haematomas. A significant proportion (60%) of these anticoagulant associated intracerebral haematomas are fatal, which is a higher fatality rate to that seen with ischemic stroke (10).

Despite having been available for over 50 years, and the clinical and patient inconvenience of the associated monitoring, it has only been in the last few years that alternatives to warfarin for the prevention of ischemic stroke in patients with atrial fibrillation have become available. These new oral drugs also interfere with clotting enzymes (such as thrombin or factor-Xa inhibitors), but as this inhibition is more specific, and as they are not affected by Vitamin K, or other factors that influence the effect of warfarin, they do not require routine monitoring.

1.3 Benefit-risk methodologies

1.3.1 BRAT

The BRAT framework was developed by Pharmaceutical Research and Manufactures of America (PhRMA) benefit-risk action team (BRAT). BRAT provides a guideline on organising, understanding and summarising evidence of benefits and risks. The framework consists of 6 steps (see figure 2). For more information on the BRAT framework

we refer to the PROTECT WP5 Benefit-risk Integration and Representation, A systematic review and classification of Methodologies for Benefit-risk Decision-Making in Medicines (11).

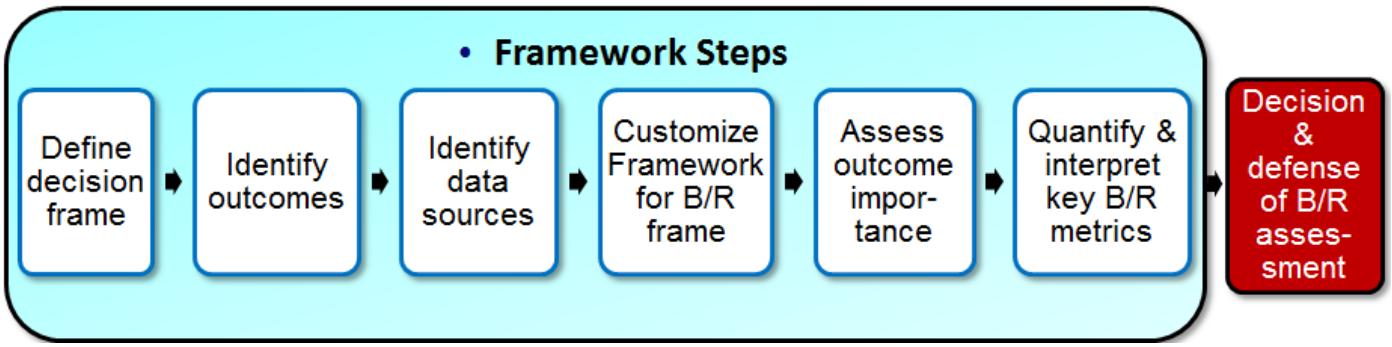


Figure 2: The 6 steps of the BRAT framework

1.3.2 SMAA

Stochastic Multi-criteria (-objective) Acceptability Analysis (SMAA) can be seen as an extension of Multi-criteria Decision Analysis (MCDA). As in MCDA, SMAA provides integrated benefit-risk weighted utility scores (overall benefit-risk score) for each alternative and ranks the different options. Understanding the principles of SMAA requires mathematical understanding of stochastic phenomena and uncertainty. The SMAA model for this case study will be implemented in the open-source software JSMAA. For more information on SMAA we refer to the PROTECT WP5 Benefit-risk Integration and Representation, A systematic review and classification of Methodologies for Benefit-risk Decision-Making in Medicines (11).

1.4 Aims and objectives

This case study aims to investigate the difficulties that may be encountered when undertaking a benefit-risk assessment for an older medicinal product with well-established use. To assess the difficulties of doing a benefit-risk assessment for an older medicine, we applied the BRAT framework (see section 1.3.1 BRAT) to a case study assessing the benefit-risk balance of warfarin for the treatment of atrial fibrillation.

We illustrated how formal benefit-risk methodologies can be applied to older medicinal products where clinical trial data to current standards may not be available. Methods to deal with the issues of the timing of benefit and risk events are also investigated. The timing issue is common in benefit-risk assessment of medicines, for example the time horizon to achieve a benefit (e.g. avoidance of ischaemic stroke) is much longer than the time horizon for a patient to experience some of the unfavourable outcomes such as bleeding. We also investigate where there is a need for a regular healthcare intervention to ensure that benefit-risk balance remains positive by measuring the impact on anticoagulation.

The benefit-risk assessment of warfarin was carried out in three stages, with increasing complexity: work stream 1 (Section 2 Work stream 1: Warfarin versus placebo/control), work stream 2 (Section 3: Work stream 2 – Warfarin versus Active Comparators) and work stream 3 (Section 4: Individual benefit risk assessments for warfarin using patient level data).

Work stream 1: In this initial stage a benefit-risk assessment of warfarin in atrial fibrillation versus the alternative of no treatment/placebo was carried out. Then an assessment of whether observational studies of warfarin treatment in atrial fibrillation were compatible with the data from the randomised clinical trials used in the initial assessment was done.

Work stream 2: Changes in the benefit-risk profile over time was considered by using the data from 3 recent clinical trial programmes for a new class of anticoagulant. Firstly we assessed whether the benefit-risk for warfarin versus the newer products was positive, and then assessed whether the warfarin clinical trial data from these new trials were compatible with the data in the first assessment.

Work stream 3: The final part of the assessment used individual patient level data to identify the benefit-risk profile for the product based on patient demographics.

2 Work stream 1: Warfarin versus placebo/control

2.1 Introduction

This section discusses the first work stream in the warfarin case study where the benefit-risk balance of warfarin is assessed and compared to that of placebo or control. The benefit-risk assessment is structured according to the BRAT framework as described in Section 1.3.1 BRAT.

The benefit-risk assessment of warfarin in atrial fibrillation versus the alternative of no treatment/placebo is presented here. We also explore the differences it would make to the benefit-risk balance when using data from observational studies compared to using data from randomised clinical trials.

2.2 Decision context

The benefit-risk assessment of warfarin will in this WS1 be against no treatment/placebo (hereafter referred to as control). The assessment will be for the primary prevention of ischaemic stroke for patients with non-valvular atrial fibrillation.

Patients with artificial heart valves were not included in this assessment as they have an even higher rate of ischaemic stroke, as a consequence of their valve as well as any concurrent atrial fibrillation and require a higher INR (2.5-3.5). A separate benefit-risk assessment would be required in this population.

2.3 Identify outcomes

The building of the value tree and identification of outcomes was an iterative process, where the value tree was customised over several iterations in order to take into account problems with data availability, double counting, and criteria comparability; this process in documented in Appendix 3: Iterative process to define value tree/effect table. In the figure below the value tree which was used as the base for the forthcoming analysis is shown. An alternate value tree was also defined (see figure 4).

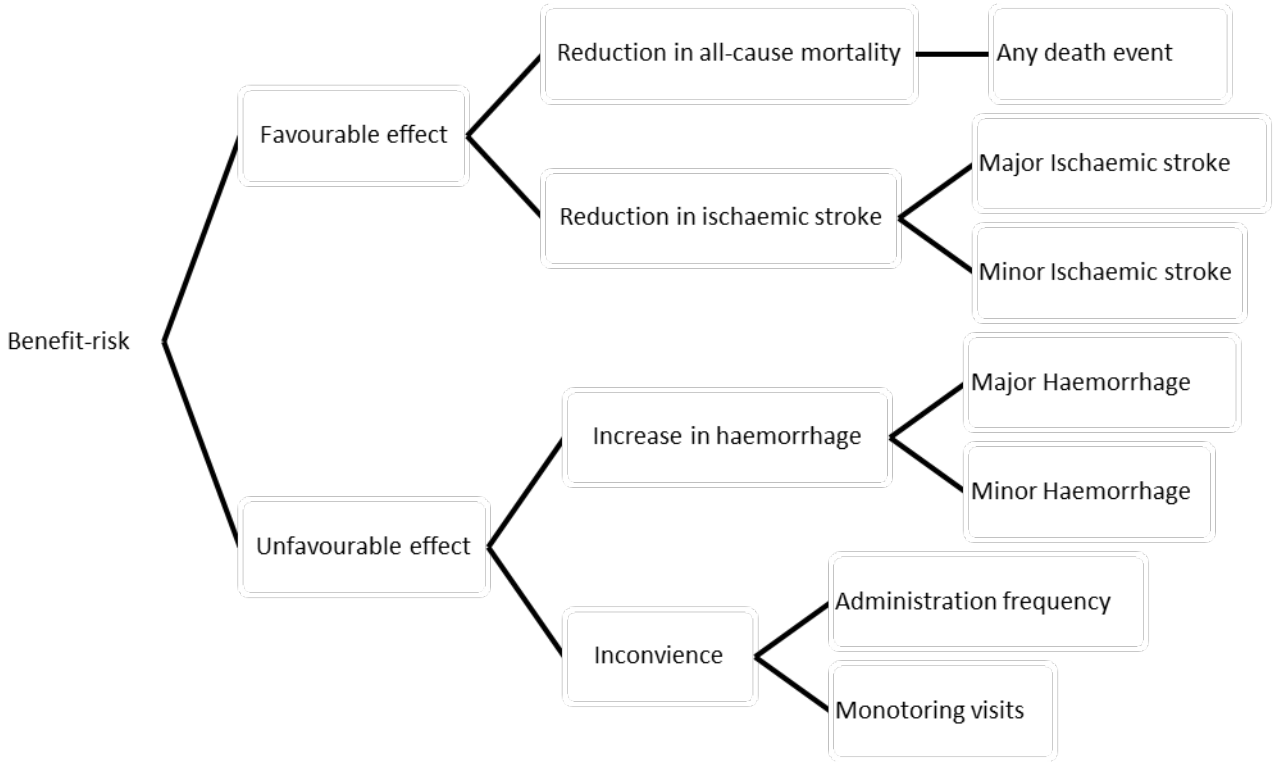


Figure 3 Value tree for the benefit-risk assessment of warfarin versus control

Reduction in all-cause mortality is a reasonable criteria to use for benefit-risk analysis as done in the primary value tree, even though it may include reduction in deaths from causes outside the licensed indication e.g. pneumonia secondary to stroke. Major Ischaemic stroke is defined as leaving disability a month after onset either with or without independent functioning, excluding fatal events. Minor ischaemic stroke is defined as events with little or no disability a month after onset. Major haemorrhage is defined as bleeding events leading to hospitalisation with transfusion, or surgery or permanent impairment, or CNS haemorrhage excluding fatal events. Minor haemorrhage events include all other non-fatal bleeding events.

Furthermore consideration was made to include criteria to account for the inconvenience to the patient of the extra monitoring required for patients on warfarin. This will be assessed in WS2 rather than WS1.

An alternate value tree was constructed for comparison. In the alternate value tree, 'Ischaemic stroke' and 'Haemorrhage' are split down into fatal, major and minor events. The haemorrhage branch of the tree has an additional group 'CNS haemorrhage'. This was done to create more comparable criteria in the benefit and risk branches. Permanent disabilities are clearly considered in 'Major Ischaemic stroke' criteria, and it is expected that they are associated with a risk aversion that is very close (if not identical) to the risk aversion expressed for the permanent disabilities due to haemorrhagic strokes. However, the criteria 'Major haemorrhage', although including disabling events, points towards severity in terms of treatment of the event and not permanent disabilities. Therefore including CNS haemorrhage events which are assumed to lead to disability would help to ensure that the value tree is not biased towards the benefit side. The parameterisation of this alternative value tree is explored in the SMAA model in section 2.7.1 Exploring the benefit-risk balance using SMAA.

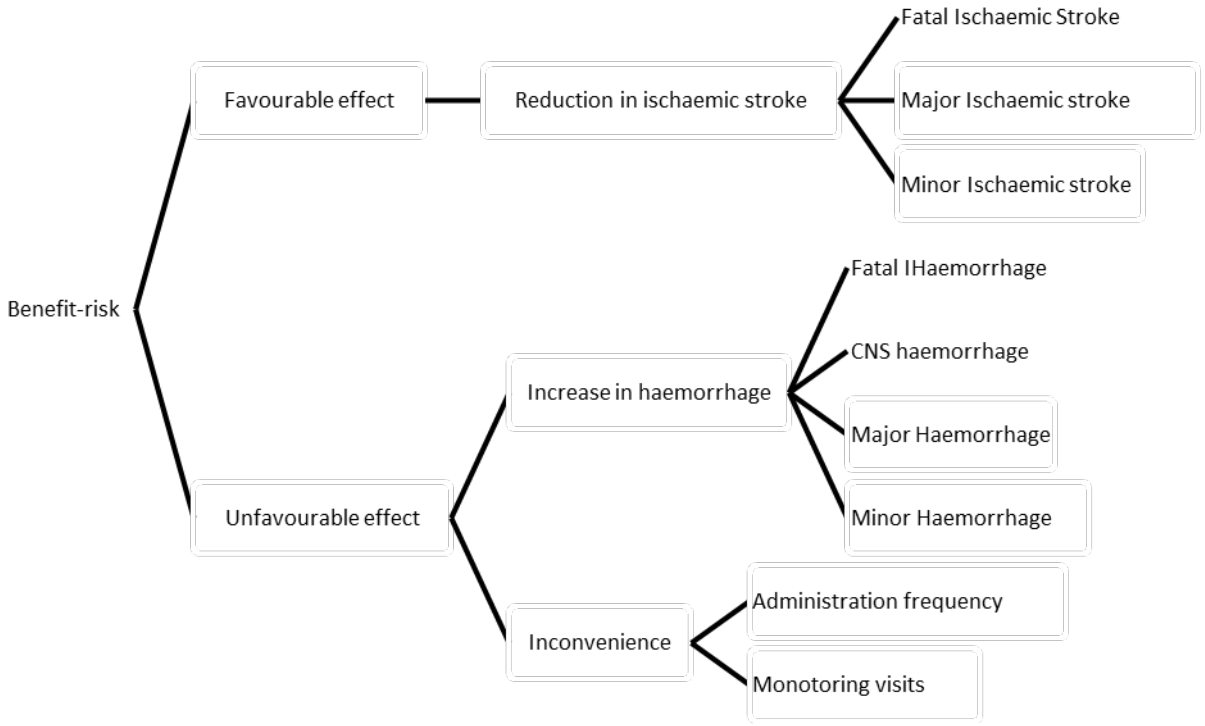


Figure 4: Alternate value tree for the benefit risk analysis of warfarin versus control

2.4 Identify and extract data sources

Data sources were identified through a systematic literature review (for more information see: Appendix1: WS1 Literature search Strategy). The literature search found several reviews and meta-analyses for the prevention of stroke in atrial fibrillation, all based on the same 5-6 randomised clinical trials (AFASAK I (12), BAATAF (13), CAFA (14), SPIN I (15), SPINAF (16) and EAFT (17). For this analysis data (AFASAK I (12), BAATAF (13), CAFA (14), SPIN I (15) and SPINAF (16) are used since they all are for the primary prevention of stroke in atrial fibrillation. The EAFT (17) study endpoint is secondary prevention of stroke in atrial fibrillation and will not be included. All studies are summarised in Appendix 2: Summary of randomised clinical trials.

Table 1: Effects table data from RCTs (only direct comparison warfarin vs control (placebo blinded and un-blinded) primary prevention of stroke, atrial fibrillation.

	Category	Outcome	Study	Duration	Warfarin		Control	
				years	cases	total	cases	total
Benefits	Reduction in all-cause mortality	All-cause mortality*	AFASAK I	1.2	20	335	28	336
			BAATAF	2.2	11	212	26	208
			CAFA	1.3	10	187	8	191
			SPAF I	1.2	6	210	8	211
			SPINAF	1.7	22	281	29	290
	Reduction in ischemic stroke	Major stroke	AFASAK	1.2	4	335	7	336
			BAATAF	2.2	2	212	8	208
			SPINAF	1.7	3	260	9	265
			SPAF	1.2	2	210	7	211
		Minor stroke	AFASAK	1.2	0	335	5	336
			BAATAF	2.2	0	212	4	208
			SPINAF	1.7	0	260	9	265
			SPAF	1.2	4	210	10	211
Risk	Increase in haemorrhage	Major haemorrhage	AFASAK	1.2	1	335	0	336
			BAATAF	2.2	7	212	7	208
			CAFA	1.3	3	187	1	191
			SPINAF	1.7	7	260	4	265
			SPAF	1.2	3	210	4	211
		Minor haemorrhage	AFASAK	1.2	20	335	0	336
			BAATAF	2.2	32	212	14	208
			CAFA	1.3	2	187	0	191
			SPINAF	1.7	64	260	46	265

*Data from Aguilar study (18).

Major Ischemic stroke – disabling both with and without loss of independent function (non-fatal)

Mild ischemic stroke –Leaving little or no definite functional disability a month after onset

Major haemorrhage – Requiring medical intervention also including CNS haemorrhage (non-fatal)

Minor haemorrhages – all other (non-fatal)

Table 2: Effects table for alternate value tree, Data for Warfarin versus control (Placebo both blinded and unblended) for primary prevention of stroke in atrial fibrillation.

	Category	Outcome	Study	Duration	Warfarin		Control	
				years	cases	total	cases	total
Benefit	Reduction in ischaemic stroke	Fatal Ischaemic Stroke	AFASAK	1.2	1	335	4	336
			BAATAF	2.2	0	212	1	208
			SPINAF	1.7	1	260	1	265
			SPAF	1.2	0	210	0	211
		Major Ischaemic Stroke	AFASAK	1.2	4	335	7	336
			BAATAF	2.2	2	212	8	208
			SPINAF	1.7	3	260	9	265
			SPAF	1.2	2	210	7	211
		Minor Ischaemic Stroke	AFASAK	1.2	0	335	5	336
			BAATAF	2.2	0	212	4	208
			SPINAF	1.7	0	260	9	265
			SPAF	1.2	4	210	10	211
Risk	Increase in Haemorrhage	Fatal Haemorrhage	AFASAK	1.2	1	335	0	336
			BAATAF	2.2	1	212	1	208
			CAFA	1.3	2	187	0	191
			SPINAF	1.7	0	260	1	265
			SPAF	1.2	1	210	0	211
		CNS Haemorrhage	BAATAF	2.2	0	212	0	208
			CAFA	1.3	0	187	0	191
			SPINAF	1.7	1	260	0	265
			SPAF	1.2	1	210	2	211
		Major Haemorrhage	BAATAF	2.2	7	212	7	208
			CAFA	N/A	3	187	2	191
			SPINAF	1.7	6	260	3	265
			SPAF	1.2	2	210	2	211
		Minor Haemorrhage	AFASAK I	1.2	20	335	0	336
			BAATAF	2.2	32	212	14	208
			SPINAF	1.7	64	260	46	265

Major Ischemic stroke – disabling both with and without loss of independent function (non-fatal)
Mild ischemic stroke –Leaving little or no definite functional disability a month after onset
CNS Haemorrhage – Excluding fatal events
Major haemorrhage – Requiring medical intervention excluding CNS haemorrhage (non-fatal)
Minor haemorrhage – all other (non-fatal)
N/A – data not available

To relate the data from randomised clinical trials to actual clinical practice, data from several observational studies are included for comparison to RCTs data. It is not always possible to identify the outcome found in the RCTs in the observational studies, therefore broader defined outcomes were used in some circumstances. The studies presented here are not exhaustive, they are the studies identified in the initial literature search. This search was designed to

identify reviews or meta-analysis of randomised clinical trials treating patients with warfarin for the prevention of stroke in atrial fibrillation. However the purpose of this study is not to do a complete benefit-risk analysis of warfarin but rather to assess the difficulties of doing a benefit-risk assessment for an older medicine. The extent to which this benefit risk assessment depends on particular sources for data, either for validation of old study data or for validation of observational data will help to inform what specific difficulties may arise when considering the benefit risk of an older product.

In the observational studies identified it was always possible to extract information on the event rates of warfarin for the criteria defined in the value tree. To the extent possible, criteria defined in the value tree were used but additional criteria were identified in order to take all the evidence into account, e.g. ischaemic stroke (which include all ischaemic stroke events).

Table 3: Effects table – Data from observational studies

		Study	Mean study duration (years)	cases	total
Benefit	All-cause mortality	Jacobs2009 (19)	1.0	18	90
	Ischaemic stroke	Kalra2000 (20)	1.9	6	167
		Darkow2005 (21)	1.3	183	4895
		Go2003 (22)	2.0	141	6320
		Caro1999 (23)	2.5	4	87
	Major Ischemic stroke	Gottlieb1994 (24)	2.1	5	186
Risk	Major haemorrhage	Kalra2000 (20)	2.1	5	167
		Gottlieb1994 (24)	2.0	2	156
		Caro1999 (23)	2.5	3	87
		Hykel2007<80 (25)	0.8	12	319
		Hykel2007≥80 (25)	0.7	14	153
	Minor Haemorrhage	Kalra2000 (20)	2.1	18	167
		Gottlieb1994 (24)	2.0	36	186
		Caro1999 (23)	2.5	45	87

2.5 Customise framework

The value trees are customised for work stream 1 where warfarin is compared to placebo. This has resulted in the removal of the inconvenience criteria to restrict the problem to a purely medical one.

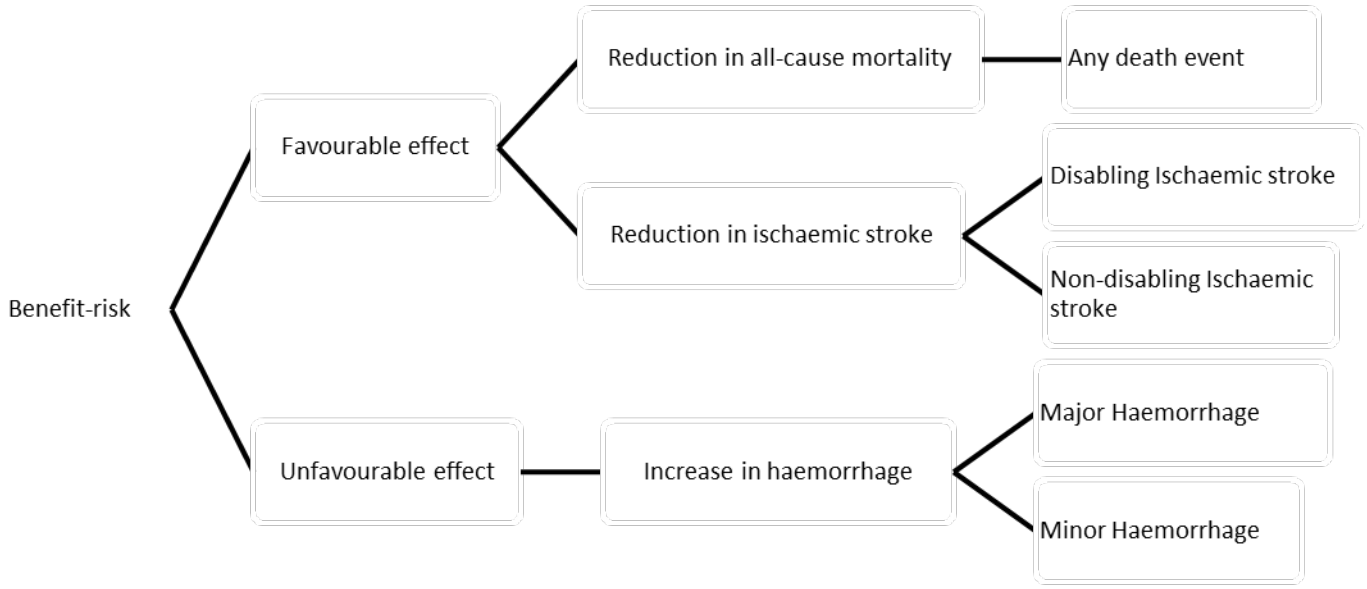


Figure 5: Customised value tree

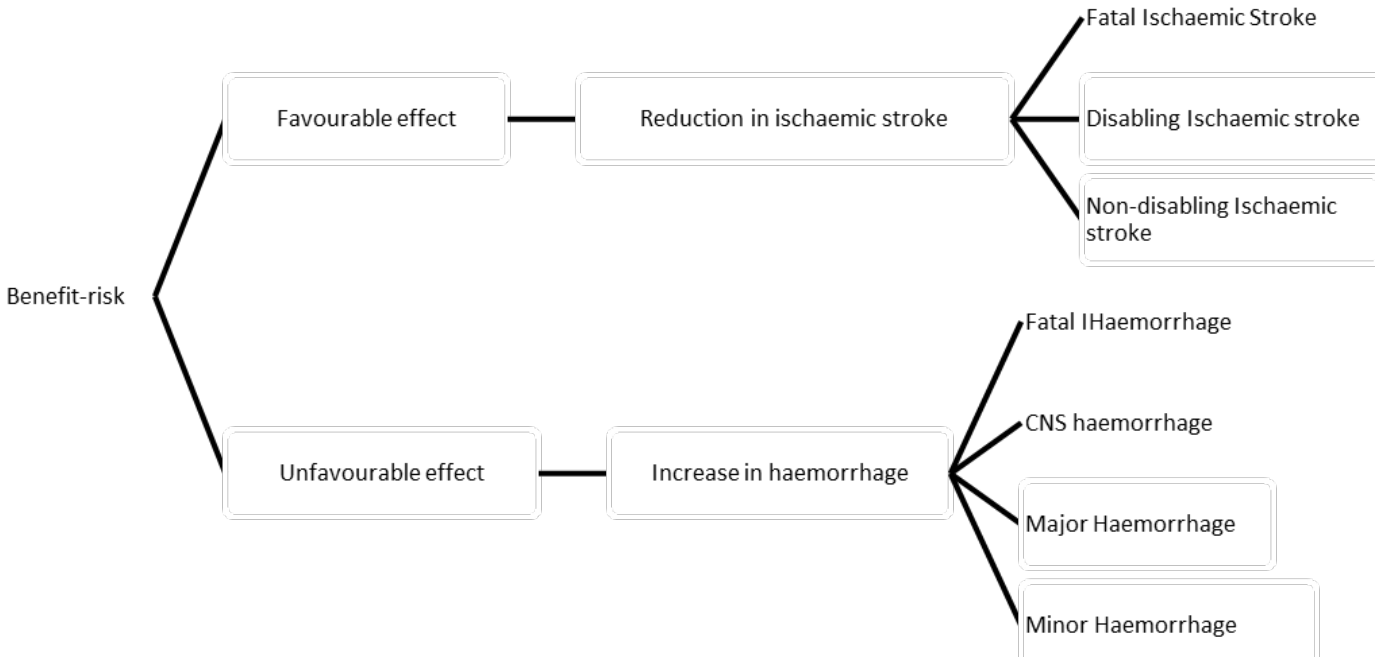


Figure 6: The customised alternate value tree

2.6 Assess outcome importance

There are several ways to assess outcome importance, and this assessment should reflect the decision-maker/makers value preferences.

For this analysis the benefit-risk criteria will be rank ordered according to utility (a subjective measure that describes preferences (satisfaction, risk attitude) for an outcome). The order will be based on the disutility value for the criteria given in the Pink 2012 study (26). The tables below give the rank order of the criteria with the top being of highest importance and the bottom one of least importance.

Table 4: Weighting criteria on ordinal scale (rank order).

Criteria	**Rank Order**	**Disutility Pink2012**(26)
All-cause Mortality	High	-
Major Stroke		0.233
Major Haemorrhage		0.1385
Minor Stroke		0.1385
Minor Haemorrhage	Low	0.06

2.7 Quantify and interpret key benefit-risk metrics

The difference in performance between warfarin and placebo for each criterion is visualised in the key benefit risk table (Table 5) and in the forest plots (Figure 7 and Figure 8). In both of them the criteria are listed according to importance (rank order given in the previous section, 2.6 Assess outcome importance - table 4).

Table 5: Key benefit-risk table for criteria in the primary value tree, the criteria are ordered according to importance, most important at the top. The colours indicate benefit criteria (green) and risk criteria (red).

Criteria	Incidence risk difference per 1000 per year	Log Peto Odds ratio
All-cause mortality	-14.7 (-28.58, -0.82)	-0.36 (-0.70, -0.07)
Disabling Ischemic stroke	-12.54 (-20.56, -4.52)	-0.97 (-1.58, -0.36)
Major Haemorrhage	2.88 (-2.42, 8.17)	0.26 (-0.38, 0.93)
Non-disabling Ischemic stroke	-12.95 (-19.34, -6.55)	-1.53 (-2.23, -0.83)
Minor Haemorrhage	44.98 (28.52, 61.45)	0.76 (0.40, 1.08)

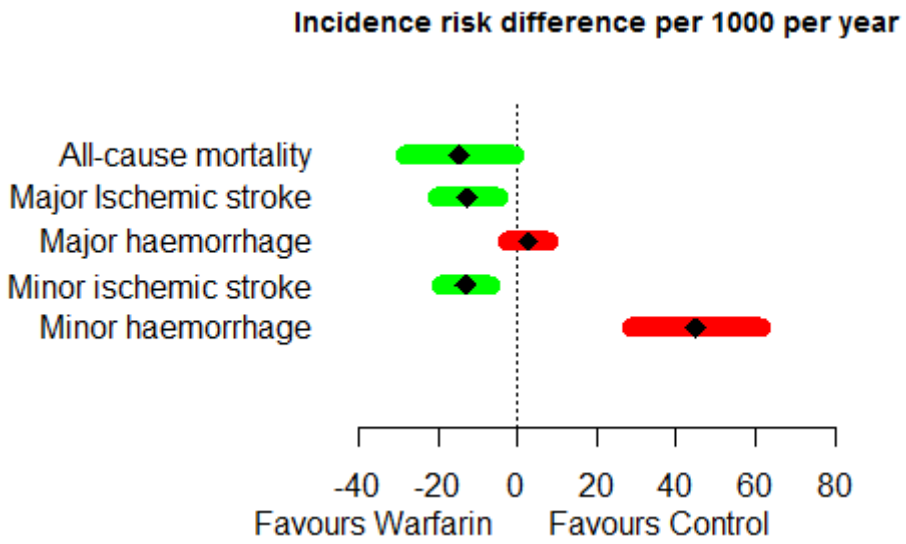


Figure 7: Forest plot illustration of the difference in consequence using risk difference per 1000 patients per year for each criteria in the value tree, the criteria are listed in order of importance (highest rank at the top).

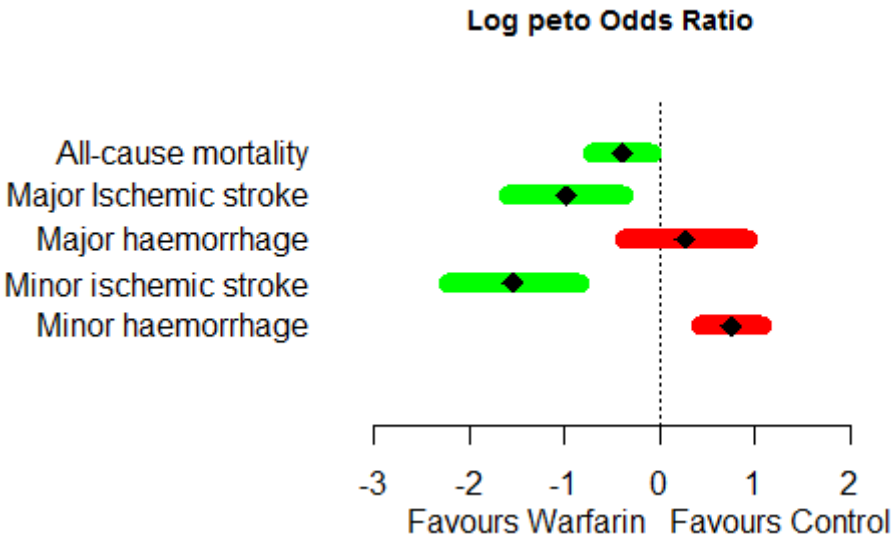


Figure 8: Forest plot illustration of the difference in consequence using the log odds ratio for each criteria in the value tree.

For the alternative value tree the difference in consequence for warfarin and control on all criteria is displayed in the forest plot (see figure 9).

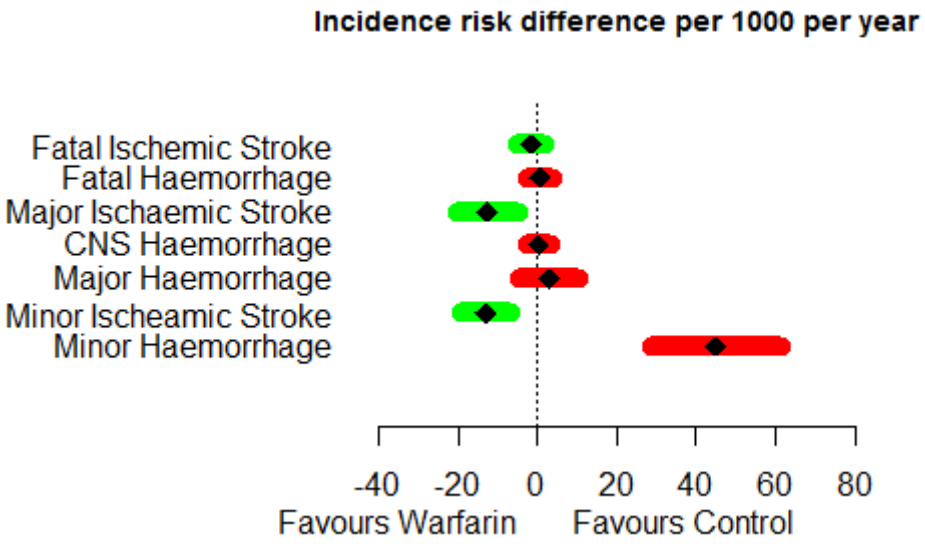
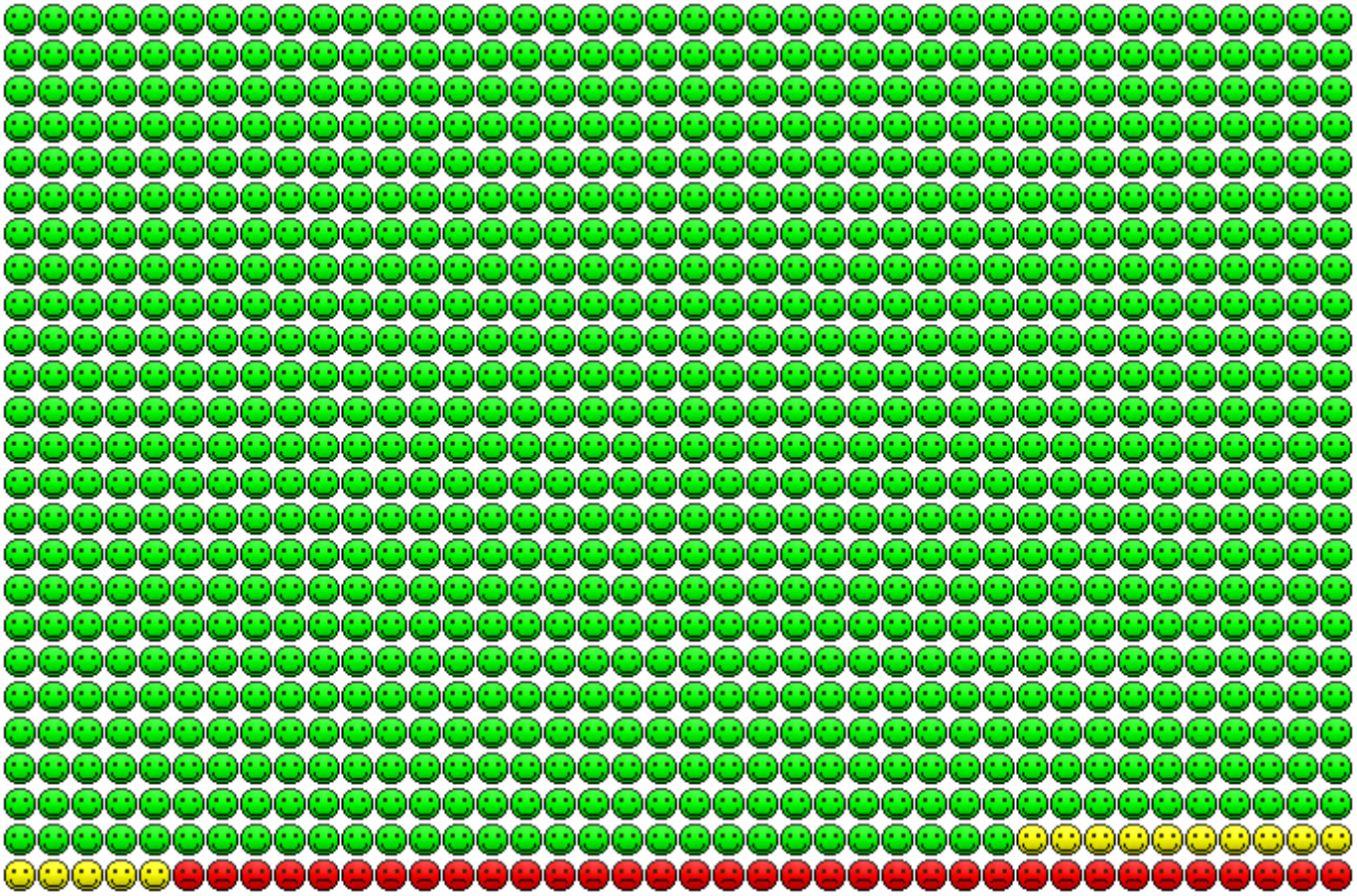


Figure 9: Forest plot visualising the difference in consequence for each criteria in the alternate value tree.

For the purpose of patient communication a pictogram is chosen as a basis for the individual benefit-risk decision. As an illustration, the criteria 'all-cause mortality' was chosen due to its high importance.



Patients who will not die from any-cause over a course of 1 year whether they take warfarin or not

Patients who will die from any-cause over a course of 1 year whether they take warfarin or not

Patients who will be saved from dying by any-cause over a course of 1 year by taking warfarin

50 patients with atrial fibrillation out of a 1000 will die from any-cause over a course of 1 year without taking warfarin compared to 35 patients out of 1000 who will die from any-cause over a course of 1 year while taking warfarin.

Figure 10: The pictogram represents the performance of warfarin versus placebo/no treatment for patients with atrial fibrillation on all-cause mortality. The data is based on meta-analysis; the mortality rate averaged 5% per year in control group (18).

2.7.1 Exploring the benefit-risk balance using SMAA

The more qualitative (semi-quantitative) approach where the outcome is visually compared in a forest plot or by the summary effect estimates for each outcome, as in Section 2.7 above, can be supplemented with a quantitative approach. Here we have chosen the Stochastic Multi-criteria (-objective) Acceptability Analysis (SMAA). SMAA builds on Multi-criteria decision analysis (MCDA), and through Monte-Carlo simulation takes into account the uncertainty represented in data. This approach was chosen due to the high uncertainty related to the point estimates and to investigate the effect of different preferences. To go through the details of the SMAA analysis, see Appendix 4:

SMAA analysis using JSMAA software. We explored some of the questions raised in connection to the alternative value tree in Section 2.1.2 in these analyses.

The SMAA method has the advantage that the analysis can be carried out with missing and unknown weights, and weighting on an ordinal and a cardinal scale. The criterion "Major Haemorrhage" was not consistently defined across studies, and may or may not be disabling. Consequently, preferences assigned to the criterion may have greater uncertainty. The SMAA analysis can give us a better understanding of the impact of different preferences and their uncertainties on the benefit-risk balance. Two different weight scenarios were explored:

Scenario A: The weight on each criterion corresponds to the disutility assigned in the Pink paper from 2012 (26). The criteria "all-cause mortality" was not reported in the Pink 2012 analysis (26), and for this scenario we assume a value of 0.4. (See table 6)

Scenario B: Criteria "Disabling Ischaemic Stroke" and "Major Haemorrhage" are assumed to carry the same weight. This is equivalent to assuming all "Major Haemorrhage" events are disabling (See table 7).

Since the weights from the literature disregard value functions for individual's disutility, they essentially already implicitly accounted for both weights and utilities. The value functions and data to be used in our SMAA model may be different to the ones accounted for in the literature, and therefore we need to 'normalise' the disutility values so that the total adds up to 1. This ensures that the weights and utilities in the final SMAA model match to the ones from the literature. To further explore the typical preference profile of a decision-maker in relation to treatment options, we conduct an analysis using missing weights assuming that these weights are uniformly distributed between values of 0 and 1.

Normalising weights for use in SMAA model

Scenario A: The weights are elicited directly based on the relative relationship of the disabilities described in the Pink 2012 study (26). The disutility for 'all-cause mortality' was not given in the Pink 2012 study(26), and here it is assigned the disutility value of 0.4. The normalised disutility values that act as a constraint to the SMAA model are given in Table 6.

Table 6: Overview of the weights on five criteria for scenario A. The criteria are weighted according to Pink2012(26) disutility values; it is assumed that the disutility values give the relative difference between one extra event in any of the criteria.

Criteria	Importance	Disutility Pink2012(26)	Normalised*
All-cause Mortality	High	0.4 †	0,41
Disabling Ischaemic Stroke		0,233	0,24
Major Haemorrhage		0,1385	0,14
Non-disabling Ischaemic Stroke		0,1385	0,14
Minor Haemorrhage	Low	0,06	0,06

† Not from Pink2012

* Normalised weights are calculated as the proportion of its disutility to the total disutility

We can then calculate the overall BR score as:

$$\text{Overall BR score} = x_0 + \sum_{i=1}^{n} \frac{w_i}{w_0} \times x_i$$

where x_0 and w_0 are the value and the normalised weight of the key event ('all-cause mortality'), and $x_i\ (i = 1,2,\dots,n)$ and $w_i\ (i = 1,2,\dots,n)$ are the values and the normalised weights of other events. From the table above for scenario A, the overall BR score can be expressed as follows:

Overall BR score = ('All-cause Mortality') + (0.58 x 'disabling Ischaemic Stroke')
+ (0.35 x 'Major Haemorrhage") + (0.35 x 'Non-disabling Ischaemic Stroke')
+ (0.15 x 'Minor Haemorrhage")

Scenario B: All "Major Haemorrhages" are considered to be disabling with or without loss of independent function (as "Disabling Ischaemic Stroke"). Table 7 shows how the weights to be assigned to the criteria in this scenario were modified from Pink (24), alongside their normalised values for the subsequent SMAA model.

Table 7: Overview of the weights on five criteria for scenario B. The criteria weighs are based on Pink2012(26) disutility values; As for scenario A the disutility value for "All-cause mortality" is not from Pink. In this scenario B, the disutility of "Major Haemorrhage" is set to be equal to "Disabling Ischaemic Stroke".

Criteria	Importance	Disutility Pink2012(26)	Normalised*
All-cause Mortality	High	0.4†	0,376
Disabling Ischaemic Stroke		0,233	0,219
Major Haemorrhage		0,233 †	0,219
Non-disabling Ischaemic Stroke		0,1385	0,13
Minor Haemorrhage	Low	0,06	0,56

† Not from Pink2012

* Normalised weights are calculated as the proportion of its disutility to the total disutility

As previous described for scenario A

Overall BR score = ("All-cause Mortality") + (0.58 x "Disabling Ischaemic Stroke")
+ (0.58 x "Major Haemorrhage") + (0.35 x "Non-disabling Ischaemic Stroke")
+ (0.15 x "Minor Haemorrhage")

The overall BR score in this scenario is more influenced by the changes in the value of "Major Haemorrhage" compared to scenario A. Additionally, the weights used in scenario B will consistently produce an overall BR score that is at least as high as that in scenario B. This implies that scenario A fits the preference characteristics of decision-makers who are more risk averse when compared to scenario B.

SMAA analysis

Given our model we find, from the SMAA analysis of scenario A, that the probability for warfarin to come out best compared to control is nearly 1. For scenario B our analysis does not show a significant change, giving a probability of about 0.99 that warfarin will come out best compared to control.

To further explore the possible outcomes of the benefit-risk model, an analysis using missing weights was done. From this we can determine the central weight vector for each alternative that is ranking best. The warfarin central weight will be denoted Scenario (W) and the control central weight will be denoted Scenario (C).

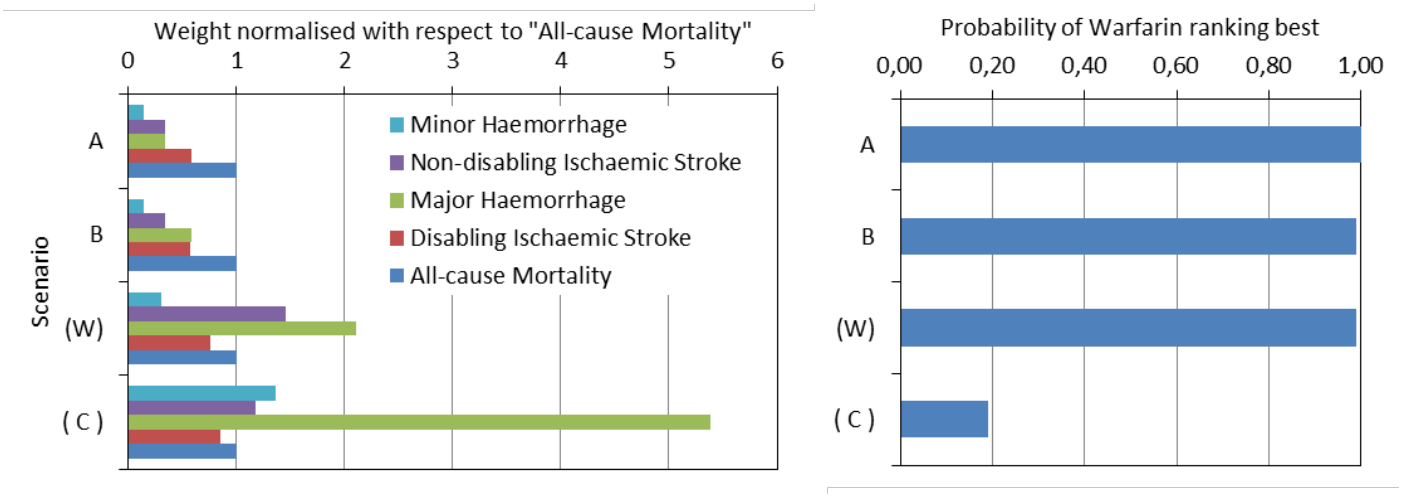


Figure 11: To the right the weights for each endpoint normalised with respect to "All-cause Mortality" for the four different scenarios, and to the left the probability of warfarin ranking best under the four different scenarios

The SMAA analysis suggests that there is a fairly wide weight space where warfarin will have a high probability of having the best overall benefit-risk score. The missing weight analysis showed that even with a major haemorrhage event having a weight of more than double of the weight of a mortality event or a disabling ischaemic stroke event, there is a very high pobability of warfarin having the best overall benefit-risk score (around 0.99 or 99 percent).

To put this in another way, we need to have one minor haemorrhage event weighting more than a mortality or disabling ischaemic stroke event, and a major haemorrhage event having several fold higher weight than mortality or disabling stroke event to overturn the positive benefit risk balance for warfarin in atrial fibrillation

2.8 Uncertainty

This benefit-risk assessment for a well-established product has some areas of uncertainty despite the number of years of warfarin experience, and the very large number of patients who have used the drug. The age of the product means that there is uncertainty over the quality of the early clinical trials, conducted in the early 1990s, which may not reflect current standards. However, even within older trials the impact of being in a clinical trial setting may improve compliance, and hence the results versus placebo may not be transferable to the results versus no treatment. Additionally, warfarin is a difficult drug to use and monitor, and the experience from clinical trials may not reflect clinical practice. For example, patients in clinical trials may have better INR control and closer INR monitoring and patient education than patients in clinical practice. In view of the impact of the drug-drug and drug-food interactions on the INR, which is a critical measure for the efficacy of warfarin, it is unknown what impact this may have on the benefit-risk assessment. Furthermore the age of the patients in clinical trials is lower than those in the actual clinical practice (see WS3).The percentage of patients with other medical conditions such as diabetes, previous transient ischemic attack, and congestive cardiac failure are lower in the clinical trials compared to the

actual clinical practice. The risk of both ischaemic and haemorrhagic stroke increases with age and hence the benefit-risk balance may change as patients get older. As with the lower INR control, seen in actual clinical practice compared to clinical trials, age and other medical conditions could also influence the benefit-risk balance. However, this impact is unknown. Additionally, this is a lifelong treatment and the benefit-risk balance may therefore change for an individual patient over time.

To compare the events rate (Figure 12) for observational studies and RCTs, it is relevant to look at differences between studies. Figure 13 below shows the intended INR target range for the difference between observational studies and the RCTs together with the actual time spend in the target (TTR, %). It is also relevant to compare other study characteristics when looking at the events rates for warfarin in the different studies; this is done in table 8 and for a quick overview, in figure 14.

Below we compare the performance of warfarin on the benefit and risk criteria in the different observational studies and RCTs.

For the endpoint all-cause mortality (Figure 12 A) there is minimal overlap between the RCTs and the observational study (19). This observational study is the only one to state this endpoint, however differences between the observational study and the RCTs could be explained by the difference in mean age, which is between 64 and 68.5 years in the RCTs and 83 years in the Jacobs study (19).

To compare the event rates of ischaemic stroke in the RCTs and observational studies, we look at the observations disabling ischaemic stroke (see Figure 12 C), which is also a critieria in our benefit-risk analysis. This endpoint was reported only in one of the identified observational studies. Therefore, a comparison is also made for the endpoint all ischaemic strokes (see Figure 12 B). The event rate for ischaemic stroke of warfarin-treated patients in the clinical trials reflects fairly well the event rate seen in the observational studies. Both for the RCTs and the observational studies, there is some between-study variation, some of this variation may be explained by the difference in study characteristics, which will be investigated further in WS3.

For the risk criteria major haemorrhage (see Figure 12 D), the Hykel study (25) stands out as different from the other studies, a high rate of major haemorrhage is observed, however the patients in this study are older than the patients in the RCTs. Additionally, the two groups in the Hykel study (25) have higher prevalence of hypertension. In the minor haemorrhage (see Figure 12 E), there is some between-study variation both between the RCTs results and between results from RCTs and observational studies, again some of this could be explained by differences between study population characteristics. Again this will be explored further in WS3.

Overall the efficacy and safety seen in the RCTs is reflected fairly well in the observational studies, and will not change the benefit-risk profile for patients with atrial fibrillation. The comparison does reveal some possibilities for a different benefit-risk profile in specific patient groups e.g. by age or hypertension status, and this will be explored further in WS3.

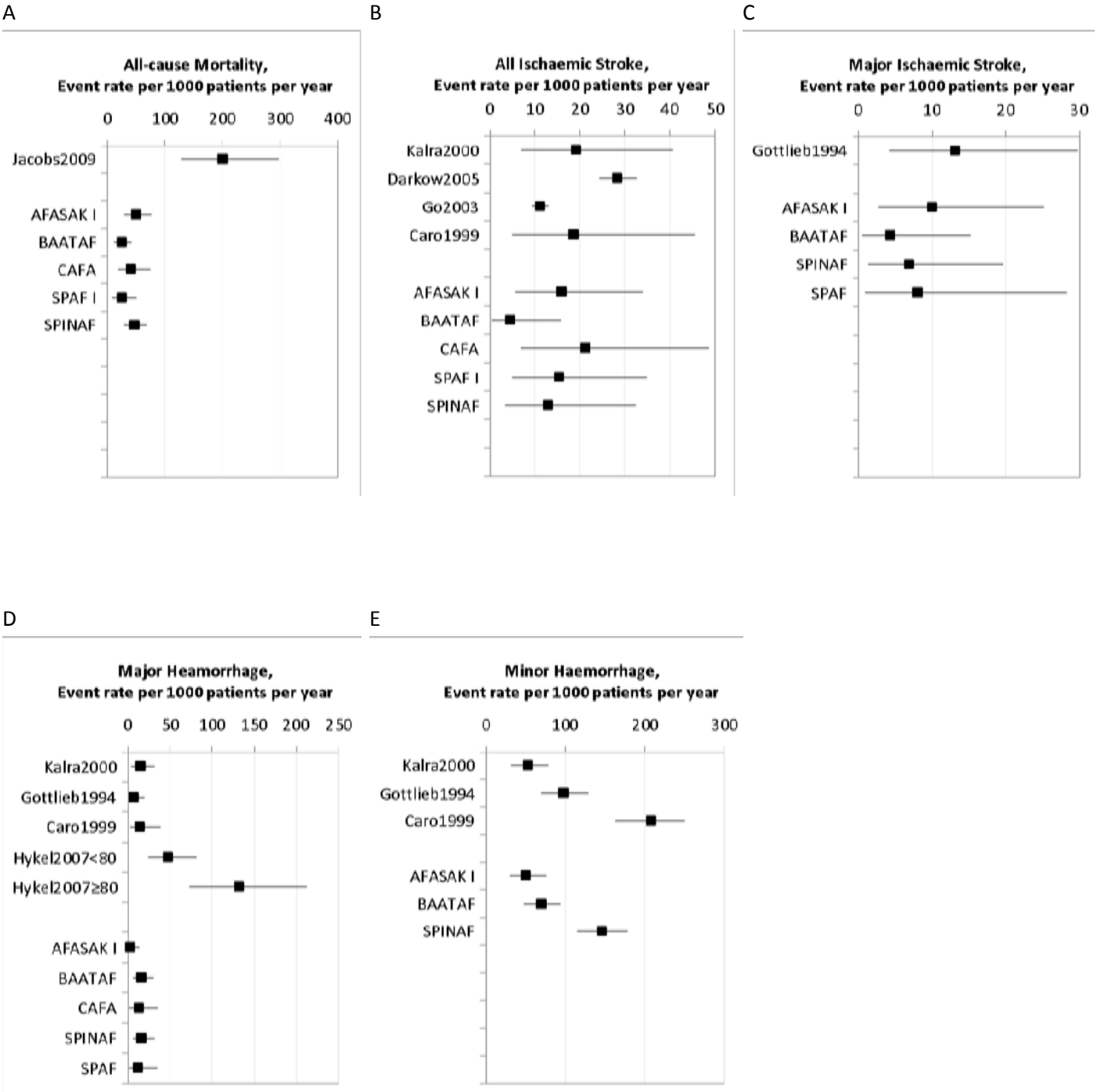


Figure 12 : Events rates for warfarin in observational studies and RCTs, for comparison.

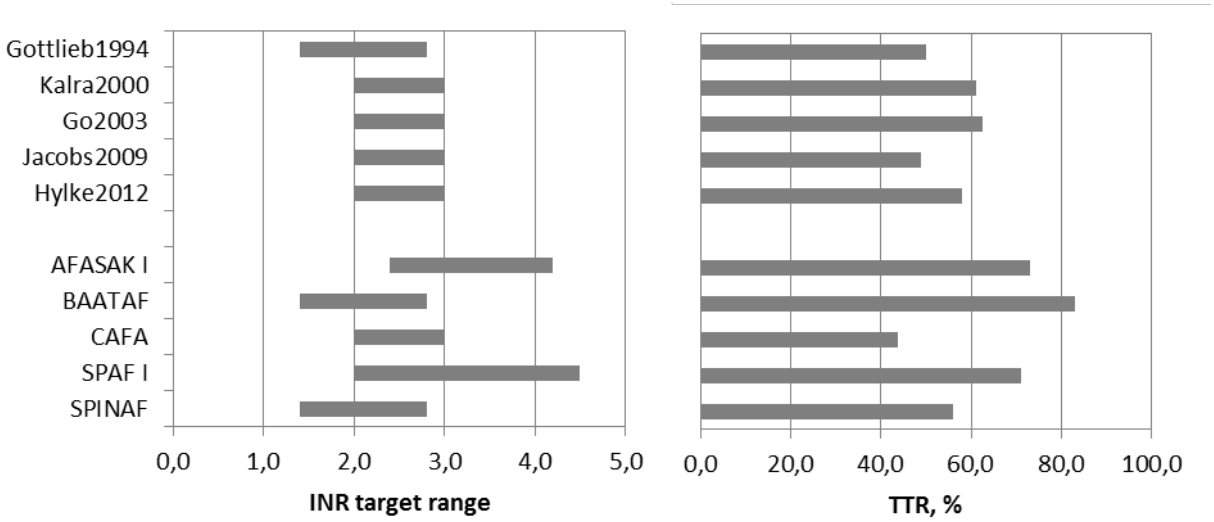


Figure 13: To the left INR target in observational studies (at the top) and RCTs (at the bottom) and time spent in target range (TTR, %) in the right figure.

Table 8: Study characteristics for RCTs and observational studies

Study	Mean age, y	Gender, male, %	Prior stroke, %	Diabetes, %	Hypertension, %	Heart Failure, %	Angina, %
AFASAK I	-	53	5	7	32	50	19
BAATAF	68.5	75	3	14	51	24	23
CAFA	68	75.9	3.2	13.9	43.3	23.5	21.9
SPAF I	64	74	8	12	49	N-	-
SPINAF I	67	100	-	17	55	31	22
Gottlieb1994	87.7	66	27	26	53	42	24
Caro1999	70.8	66	21	24	43	34	21
Kalra2000	77	40	14	15	43	20	-
Go2003	71	59.2	10.9	18.2	51.6	33.1	-
Darkow2005	79.8	45.5	6.2	17.3	37.1	-	-
Hylek2007(<80)	73	57	3	19	71	23	-
Hylek2007(>80)	84	45	9	24	83	37	-
Jacobs2011	82	22	-	-	-	-	-

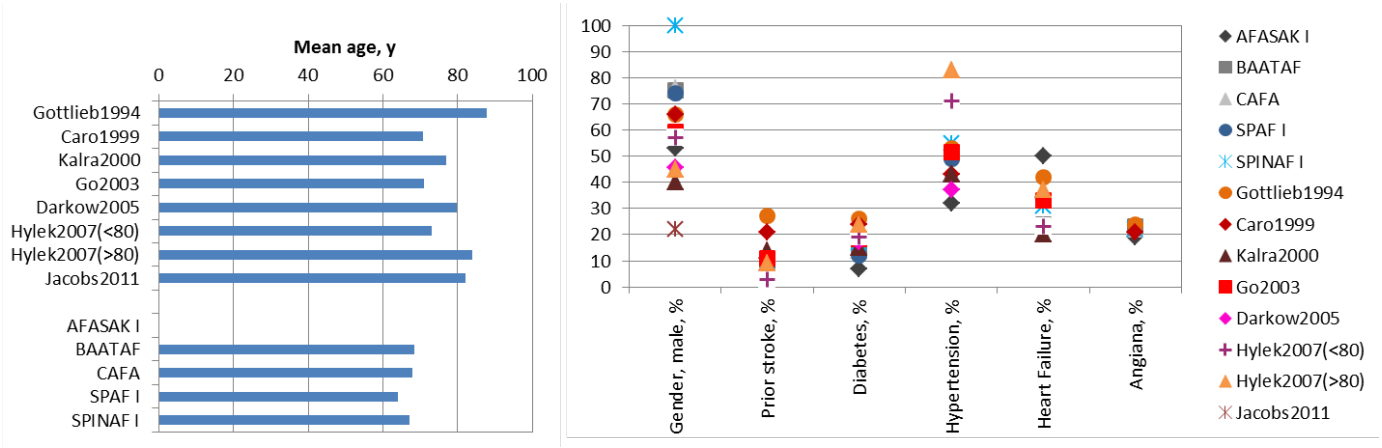


Figure 14: The bar chart to the left illustrates the mean age of the study population in different studies. The figure to the right gives a quick overview of studies with a different prevalence of some risk factors in the study population, grey-bluish colours are RCTs and reddish colours are observational studies.

2.9 Decision and communication of benefit-risk assessment

The benefit-risk balance of warfarin versus no treatment for the protection of stroke in the indication of atrial fibrillation is considered to be in favour of warfarin. This conclusion is based on the performance of warfarin compared to no treatment in the benefit criteria; 'All-cause Mortality', 'Disabling Ischaemic Stroke' and 'Non-disabling Ischaemic Stroke' and the risk criteria; 'Major Haemorrhage' and 'Minor Haemorrhage'. For the most important criterion 'all-cause mortality', the clinical studies indicate a reduction of about 15 events per 1000 patients per year (95% CI interval 0.82 – 28.58 per 1000 patients per year) with warfarin compared to control. The outcome 'Disabling Ischaemic Stroke' is also in favour of warfarin with a reduction of about 12.5 events per 1000 patients per year (95% CI interval 4.5 –20.6 events per 1000 patients per year). While there is little difference between no treatment and warfarin on the risk criterion 'Major Haemorrhage', there were on average a difference of 2.9 events per 1000 patients per year (95% CI interval -2.4 – 8.2 events per 1000 patients per year) in favour of no treatment/control.

The favourable effect of warfarin in reducing the occurrence of disabling ischaemic stroke compared to no treatment is unlikely to be influenced by the uncertainties related to quality of the early clinical trials or the uncertainty related to the slightly lower time in target INR seen in actual clinical practice compared to clinical trials, in view of the consistency between the results.

The absolute benefits are the prevention of 12-13 major ischaemic strokes for 1000 treated population per year as seen in figure 7 and therefore any impact of sub-optimal treatment such as excursions from the target INR or increases in the risk of haemorrhagic stroke will reduce the magnitude of the positive benefit-risk. In this regard, the net clinical benefit of warfarin, particularly in the light of the decreased absolute risk of ischaemic stroke over time, has also been assessed in a study by Singer DE, et. al.(27). This study examines the various uncertainties associated with treatment and concludes that the benefit-risk is most positive in those with the highest risk of ischaemic stroke which includes the oldest patients. However these are the group also most likely to suffer adverse consequences of serious bleeding events.

Communication of this benefit-risk assessment to patients is complicated because of the differences in patients' perception of the risks of stroke compared to bleeding events, and also because patients attached a large disutility values to the small 'absolute benefit' and 'injuries to the brain' criteria which appeared as both a benefit and a risk.

However the results suggest that it may be possible to derive some data from the published literature to allow a benefit-risk assessment to be visualised, even for an older medicine. Additionally it has been possible in this case to identify articles related to the use of warfarin in routine clinical practice, and to compare these to the results seen in clinical trials. This helps reduce much of the uncertainty in the assessment. Such data may not always be available and therefore this may impact the ability to derive robust benefit-risk assessments for older medicines. This group of medicines includes some of the most widely prescribed medicines in clinical practice.

2.10 Discussion

In work stream 1 the benefit-risk assessment of warfarin versus control was done based on data from 5 older randomised trials. The availability of data did play a role in the definition of benefit-risk criteria and the value tree (see Appendix 3: Iterative process to define value tree/effect table). A consequence of this was a grouping of endpoints into broader defined benefit-risk criteria and difficulties in trading off benefit and risk criteria. The quantitative analysis was used to test the effect of different weights for the risk criteria 'major haemorrhage' and to take into account the large uncertainty related to the small sample size of the RCTs.

The weighting of benefit-risk criteria was done based on information available in the literature. However, such information might not always be available, in this case it is also important to emphasise that the assessment of outcome importance and weight elicitation should always represent the decision maker's opinion.

Observational studies were used to evaluate if the benefit-risk balance based on data from RCTs could be considered valid in the actual practice. This analysis showed a fairly good agreement between what was observed in the RCTs and in the observational studies, but also flagged that some groups (e.g. high age > 80 years) might have a less favourable benefit-risk from taking warfarin. This will be investigated further in WS3. Additionally, it should be emphasised that the observational studies evaluated in this study do not represent an exhaustive review of studies from the published literature.

3 Section 3: Work stream 2 – Warfarin versus Active Comparators

3.1 Introduction

This section discusses the second work stream in the warfarin case study where the benefit-risk balance of warfarin is assessed and compared to new active comparators. The benefit-risk assessment is structured according to the BRAT framework as described in Section 1.3.1 BRAT.

The benefit-risk assessment of warfarin in atrial fibrillation versus the alternatives rivaroxaban, apixaban and dabigatran is presented here. We also explore the differences it would make to the benefit-risk balance when using warfarin data from new randomised clinical trials compared to using data from the older warfarin randomised clinical trials.

3.2 Decision context

Until recently warfarin was the only licensed anticoagulant for the indication of stroke prevention in patients with atrial fibrillation. Newer therapies have recently become available, with more specific and more direct effects on the coagulation process, such as factor Xa inhibitors (including rivaroxaban and apixaban) and thromin (II) inhibitors (including dabigatran), see figure 1 page 7.

These products are administered at a fixed dose, orally, without the need for monitoring. These products are not affected by vitamin K or food, and compared to warfarin, have minimal drug-drug interactions. Although these drugs appear more convenient, it is important to compare the benefits, and the risks to those of warfarin, as these drugs too are associated with bleeding related adverse events, including cerebral haemorrhages.

In WS2 the benefit-risk assessment of warfarin will be against the three newer anticoagulation agents rivaroxaban, dabigatran and apixaban. As in WS1, the assessment will be for the prevention of thrombotic stroke for patients with non-valvular atrial fibrillation. This case study is used to illustrate some of the differences in approach required for older products, where clinical trial data to current standards may not be available.

3.3 Identify outcomes

The initial value tree is the same as the on defined in WS1 (see section: 2.3 Identify outcomes).

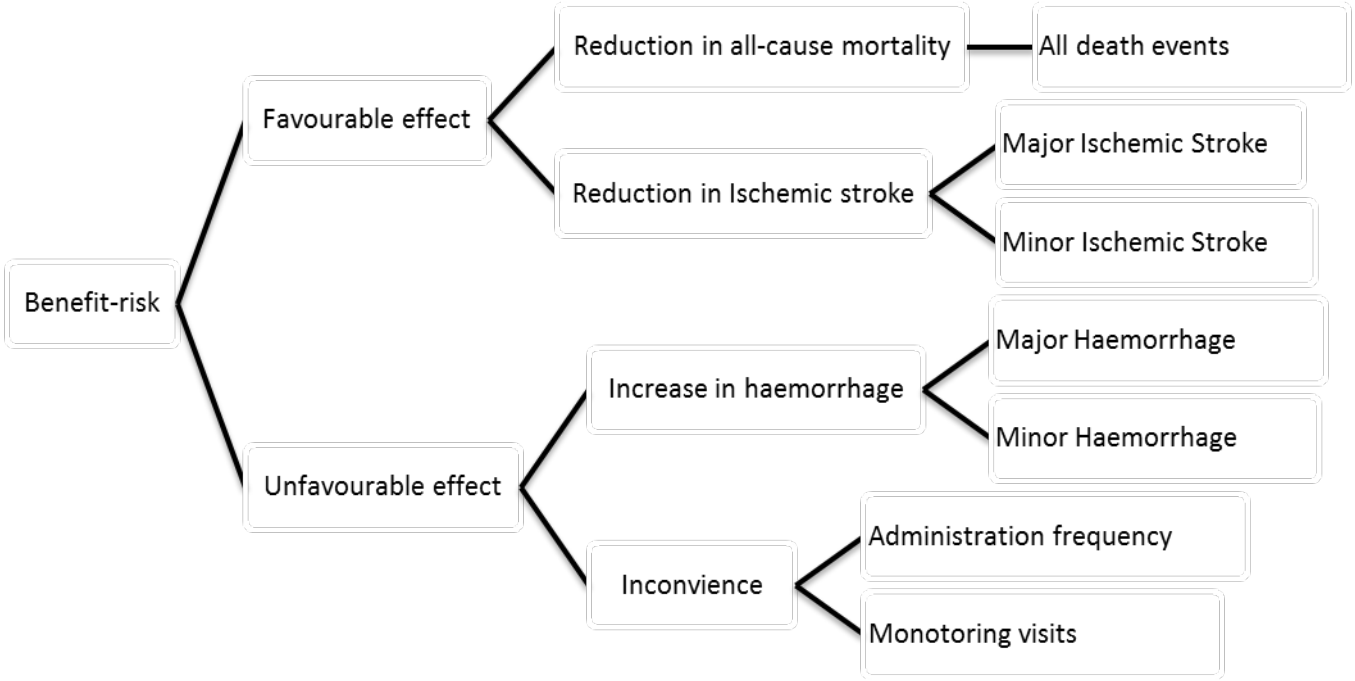


Figure 15: Initial value tree for the benefit-risk assessment of warfarin versus newer anticoagulation agents.

3.4 Identify and extract data sources

Data to analyse the clinical endpoints in the benefit risk assessment of warfarin versus rivaroxaban, dabigatran and apixaban in atrial fibrillation is based on the studies, ROCKET-AF (28), RE-LY (29, 30) and ARISTOTELES (31) respectively. For a short summary of the RTCs see section 7.2 Appendix 2: Summary of randomised clinical trials.

	Category	Criteria	Study	Comparator	Duration	Comparator			Warfarin		
					years	cases	Total	%/year	Cases	Total	%/year
Favourable effects	Reduction in All-Cause Mortality	All-cause mortality	ARISTOTLE	Apixaban	1.8	603	9120	3.52	669	9081	3.94
			ROCKET-AF	Rivaroxaban	1.9	621	7081	4.58	667	7090	4.92
			RE-LY	Dabigatran, 110mg	2.0	446	6015	3.75	487	6022	4.13
			RE-LY	Dabigatran, 150mg	2.0	438	6076	3.64	487	6022	4.13
	Reduction in Stroke	All Stroke	ARISTOTLE	Apixaban	1.8	199	9120	1.19	250	9081	1.51
			ROCKET-AF	Rivaroxaban	1.6	184	7061	1.65	221	7082	1.96
		Ischemic Stroke	ROCKET-AF	Rivaroxaban	1.6	149	7061	1.34	161	7082	1.42
			RE-LY	Dabigatran, 110mg	2.0	159	6015	1.34	142	6022	1.2
			RE-LY	Dabigatran, 150mg	2.0	111	6076	0.92	142	6022	1.2
		Fatal or Disabling Stroke	ARISTOTLE	Apixaban	1.8	84	9120	N/A	117	9081	N/A
			RE-LY	Dabigatran, 110mg	2.0	112	6015	0.94	118	6022	1
			RE-LY	Dabigatran, 150mg	2.0	80	6076	0.66	118	6022	1
		Fatal Stroke	ARISTOTLE	Apixaban	1.8	42	9120	N/A	67	9081	N/A
			ROCKET-AF	Rivaroxaban	1.6	47	7061	0.42	67	7082	0.59
		Disabling	ARISTOTLE	Apixaban	1.8	42	9120	N/A	50	9081	N/A

		Stroke	ROCKET-AF	Rivaroxaban	1.6	43	7061	0.39	57	7082	0.5
		Non-disabling Stroke	ARISTOTLE	Apixaban	1.8	115	9120	N/A	133	9081	N/A
			ROCKET-AF	Rivaroxaban	1.6	88	7061	0.79	87	7082	0.77
			RE-LY	Dabigatran, 110mg	2.0	60	6015	0.5	69	6022	0.58
			RE-LY	Dabigatran, 150mg	2.0	44	6076	0.37	69	6022	0.58
Unfavourable effects	Increase in Haemorrhage	Haemorrhagic Stroke	ROCKET-AF	Rivaroxaban	1.6	29	7061	0.26	50	7082	0.44
			RE-LY	Dabigatran, 110mg	1.2	14	6015	0.2	45	6022	0.38
			RE-LY	Dabigatran, 150mg	2.0	12	6076	0.1	45	6022	0.38
		Fatal Bleed	ARISTOTLE	Apixaban	1.8	34	9120	N/A	55	9081	N/A
			ROCKET-AF	Rivaroxaban	1.9	27	7111	0.2	55	7125	0.5
			RE-LY	Dabigatran, 110mg	2.0	23	6015	0.19	39	6022	0.33
			RE-LY	Dabigatran, 150mg	2.0	28	6076	0.23	39	6022	0.33
		Major Bleed*	ARISTOTLE†	Apixaban	1.7	380	9088	N/A	459	9052	N/A
			ROCKET-AF	Rivaroxaban	1.4	579	7111	N/A	536	7125	N/A
			RE-LY	Dabigatran, 110mg	2.0	319	6015	N/A	382	6022	N/A
			RE-LY	Dabigatran, 150mg	2.0	371	6076	N/A	382	6022	N/A
		Minor Bleed	ROCKET-AF	Rivaroxaban	1.4	1185	7111	N/A	1151	7125	N/A
			RE-LY	Dabigatran, 110mg	2.0	1566	6015	13.16	1931	6022	16.37
			RE-LY	Dabigatran, 150mg	2.0	1787	6076	14.84	1931	6022	16.37

Stroke refers to both ischemic and haemorrhagic stroke in nothing else is stated

*Include intracranial haemorrhage and exclude fatal events

†Exclude intracranial haemorrhage and include fatal events

N/A – data not available

Consideration around how patient compliance and INR compared to actual practice is discussed in WS1, the mean time in target INR range for the ROCKET-AF (28), RE-LY (29, 30) and ARISTOTLE (31) studies can be seen in table 9.

Table 9: Time in target INR for patients on warfarin in the ROCKET-AF, RE-LY and ARISTOTLE.

Study	Target INR	Mean Time I Target INR (%)	Median Time I Target INR (%)
ROCKET-AF	2.0 – 3.0	55.2	57.8
RE-LY	2.0 – 3.0	64	
ARISTOTLE	2.0 – 3.0	62.2	66

Data from ROCKET-AF (28), RE-LY (29, 30) and ARISTOTLE (31).

3.5 Customise framework

The value tree is customised as seen in figure 16. This is based on the experience from WS1. By choosing a category of "reduction in stroke" which includes both ischemic and haemorrhagic stroke, the problem of risk aversion towards disability from ischaemic stroke versus haemorrhage stroke, discussed in WS1 is avoided. However the tree does introduce a risk of double counting, since major bleeds also include haemorrhagic stroke (for ARISTOTLE (31), major bleed include fatal events but exclude intracranial haemorrhage).

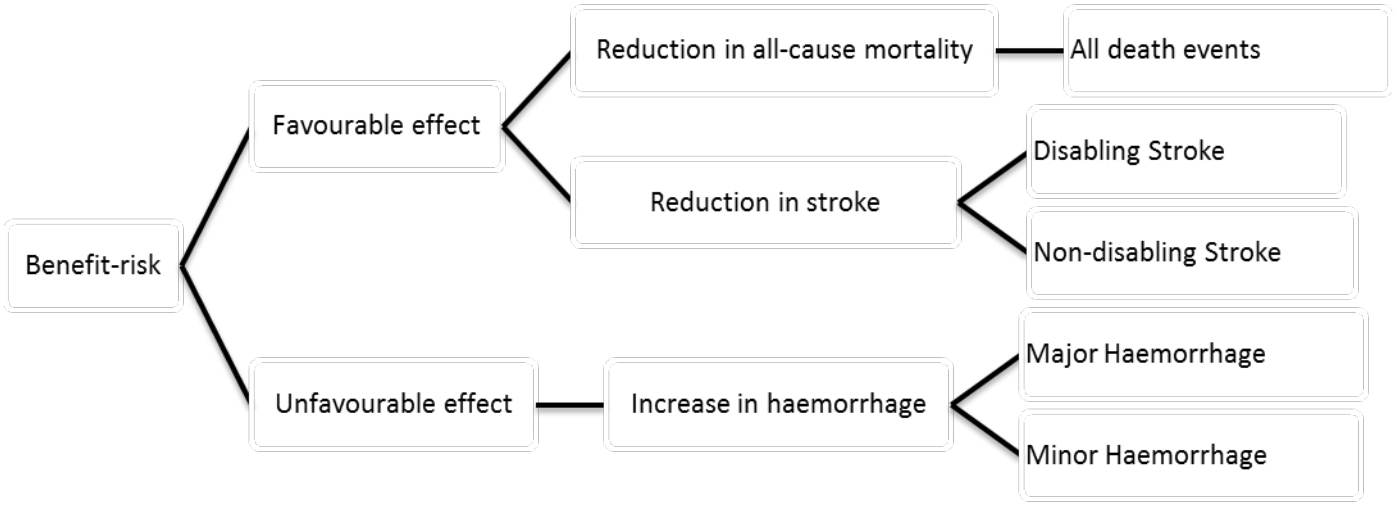


Figure 16: Customised value tree for the benefit risk assessment of warfarin versus, Rivaroxaban, Dabigartran and Apixaban.

Convenience is a difficult variable to assess quantitatively. As discussed above, patients on warfarin require regular monitoring of their dose, involving some form of blood test (though modern testing is less invasive or disruptive), requiring a healthcare professional interaction (usually a hospital-based anticoagulant service) followed by continuation or modification of the dose. Warfarin is given once daily, using coloured 1mg (brown), 3mg (blue) and 5mg tablets). Patients are instructed to take a single tablet, or combination. As half milligram tablets are rarely prescribed, patients may end up with complex, and potentially confusing regimes (such as taking a blue tablet daily, and a brown tablet on Mondays, Tuesday and Fridays). Although patient preference assessments could be used to evaluate a once daily tablet compared to the warfarin regimes with regular blood tests, the additional health burden of warfarin monitoring was not assessed explicitly. Consequently 'inconvenience' was not used in the customised model.

3.6 Assess outcome importance

As in WS1 the outcome importance is rank ordered based on the disutility values from the Pink study (26).

Table 10: Weighting criteria on ordinal scale (rank order).

Criteria	Rank Order	Disutility Pink2012 (26)
All-cause Mortality	High	-
Disabling Stroke		0.233
Major Bleed		0.1385
Non-disabling Stroke		0.1385
Minor Bleed	Low	0.06

3.7 Quantify and interpret key benefit-risk metric

3.7.1 Warfarin versus Dabigatran

Table 11: Key benefit-risk summary table for warfarin versus dabigatran, 110 mg - data from the RE-LY trial (29, 30).

Criteria	Incidence Risk Difference (IRD) per 1000 patients per year	Lower 95% CI	Upper 95%CI
All-cause mortality	3.36	-1.61	8.33
Fatal or Disabling Stroke	0.49	-1.98	2.96
Major Bleed**	5.20	0.89	9.51
Non-disabling Stroke	0.74	-1.11	2.59
Minor Bleed	30.15	20.53	39.78

** Include intracranial haemorrhage and exclude fatal events

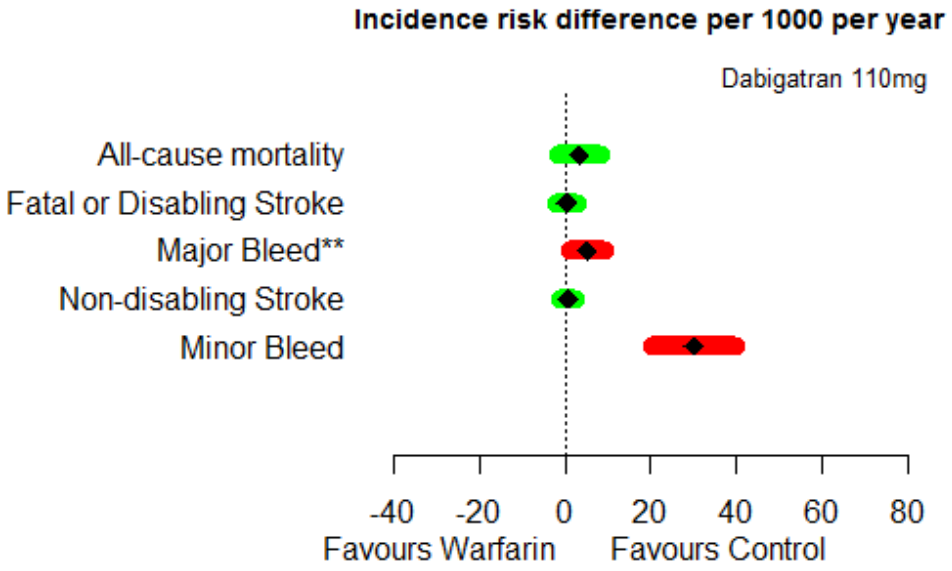


Figure 17: Forest plot displaying the risk difference per 1000 patients per year for warfarin versus dabigatran, 110 mg.

Table 12: Key benefit-risk summary table for warfarin versus dabigatran, 150 mg- data based on RE-LY trial (29, 30).

Criteria	IRD per 1000 patients per year	Lower 95% CI	Upper 95%CI
All-cause mortality	4.39	-0.54	9.32
Fatal or Disabling Stroke	3.21	0.93	5.50
Major Bleed**	1.19	-3.26	5.63
Non-disabling Stroke	2.11	0.38	3.83
Minor Bleed	13.27	3.39	23.16

** Include intracranial haemorrhage and exclude fatal events

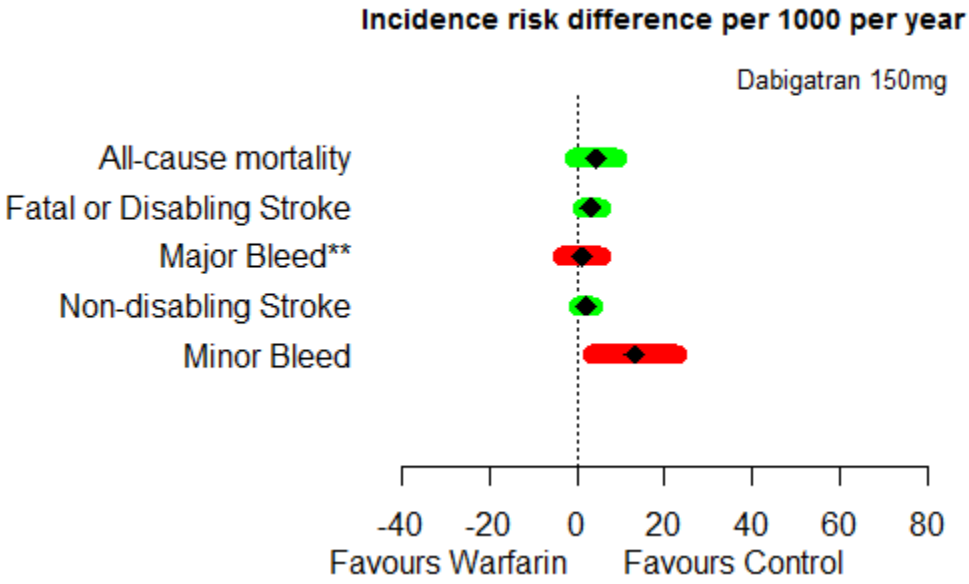


Figure 18: Forest plot of risk difference per 1000 patients between warfarin and dabigatran, 150 mg.

When interpreting the key benefit-risk table and the forest plot for warfarin versus Dabigatran 110 mg and 150 mg, it is important to take into consideration that fatal stroke events are included in both the criteria 'All-cause mortality' and 'Fatal or disabling Stroke'. Additionally, Intracranial bleeds are counted in both the 'Fatal or disabling Stroke' and 'Major Bleed' criteria.

3.7.2 Warfarin versus Apixaban

Table 13: Key benefit-risk summary table for warfarin versus apixaban – data based on ATISTOTLE trial (31).

Criteria	IRD per 1000 patients per year	Lower 95% CI	Upper 95%CI
All-cause mortality	3.97	-0.07	8.02
Disabling Stroke	0.47	-0.61	1.56
Major Bleed*	5.23	1.55	8.91
Non-disabling Stroke	1.07	-0.71	2.86
Minor Bleed	37.50	28.85	46.15

* Exclude intracranial haemorrhage and include fatal events

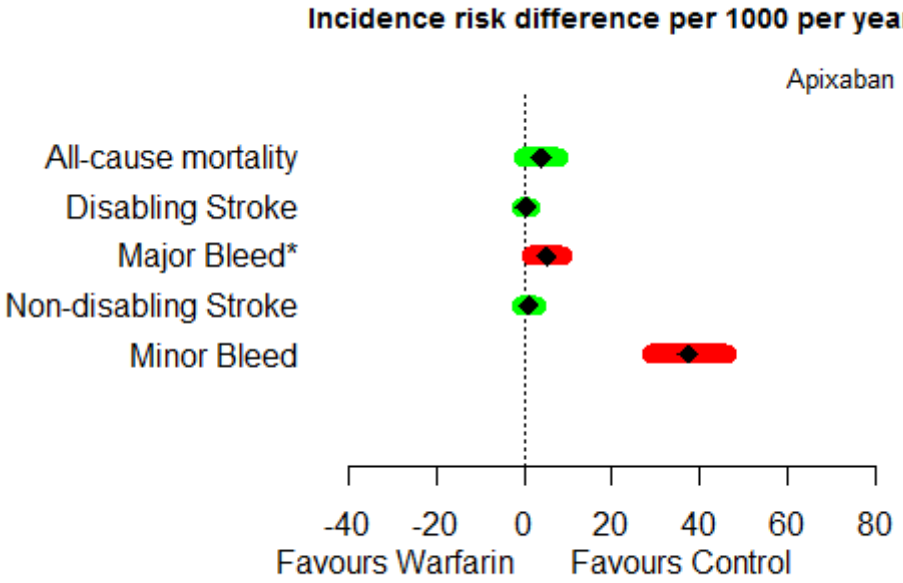


Figure 19: Forest plot, Incidence risk difference per 1000 patient per year for warfarin versus apixaban for each criterion. (Green is benefit criteria and Red is risk criteria)

When interpreting the key benefit-risk table and forest plot for warfarin versus apixaban it is important to take into consideration that fatal major stroke events are included in both the “all-cause mortality” and the “major stroke” criteria.

Figure 20: The pictogram represents the performance of warfarin versus apixaban in the indication of atrial fibrillation, on death from any cause. In the Warfarin group 74 patients out of 1000 died from any cause over 1.8 years (95% CI 68,30 - 79,04) compared to 66 patients out of 1000 in the apixaban group (95% CI 61,02 – 71,22).

3.7.3 Warfarin versus rivaroxaban

Table 14: Key benefit-risk summary table for warfarin versus rivaroxaban – data from ROCKET-AF trial (28).

Criteria	IRD per 1000 patients per year	Lower 95% CI	Upper 95%CI
All-cause mortality	3.36	-1.87	8.58
Disabling Stroke	1.22	-0.51	2.96
Major Bleed**	-3.87	-9.62	1.87
Non-disabling Stroke	-0.11	-2.40	2.18
Minor Bleed	-3.19	-11.50	5.13

**Include intracranial haemorrhage and exclude fatal events

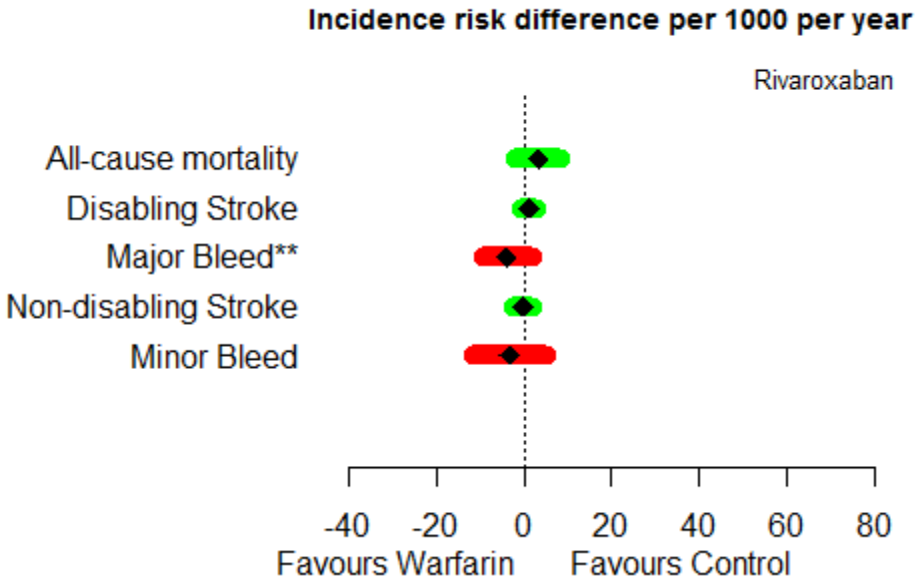


Figure 21: Forest plot showing the incidence risk difference for warfarin versus rivaroxaban in events per 1000 patients per year (green – benefit criteria, red – risk criteria)

When interpreting the key benefit-risk table and the forest plot for warfarin versus rivaroxaban, it is important to take into consideration that intracranial bleeds are counted in both the 'Fatal or disabling Stroke' and 'Major Bleed' criteria. In summary, it seems from the forest plots above that warfarin benefit criteria and risk criteria are not different from comparators apart for minor bleed in the comparison with apixaban and dabigatran (but not rivaroxaban).

3.8 Uncertainty

For warfarin versus rivaroxaban, dabigatran and apixaban, studies comparing clinical trials and actual clinical practice have not been identified.

To judge whether the profile of warfarin is similar between the early clinical studies where warfarin is compared to placebo/no treatment (WS1) and the later clinical trials where warfarin is compared to the active comparators (WS2) the events per 1000 patients per year (mean follow up duration) are plotted in a tornado diagram for all four benefit-risk criteria, for the clinical studies AFASAK I (12), BAASTAF (13), CAFA (14), SPAF I (15), SPINAF (16), ROCKET-

AF (28), RE-LY (29, 30), and ARISTOTLE (31), see figure 22. Whilst the events rates are variable, as would be expected for studies conducted over a long time period and in diverse populations, there is no evidence that the later studies are markedly different to earlier studies, and in general all the point estimates lie within the boundaries of variability from the earlier studies. Consequently it can be hypothesised that the warfarin results from the WS2 studies will be applicable to WS1. It would appear from the studies conducted that the benefit-risk profile for warfarin is worse than that for the newer anticoagulants.

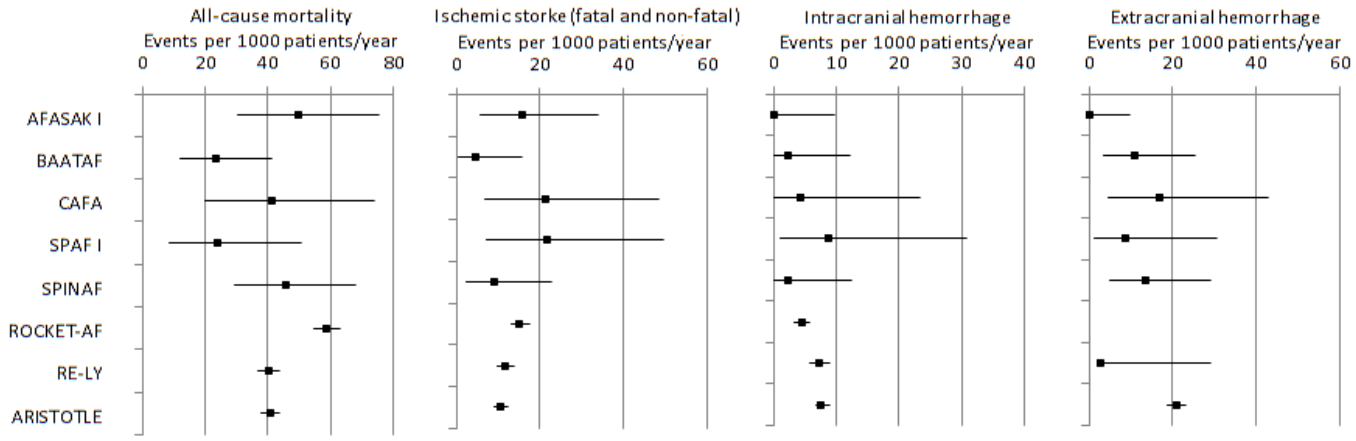


Figure 22: Warfarin profile between WS1 and WS2. Number of events per 1000 patients/mean follow-up year for warfarin in the four benefit-risk criteria. Event rate and corresponding 95% CI calculated using Clopper-Pearson method.

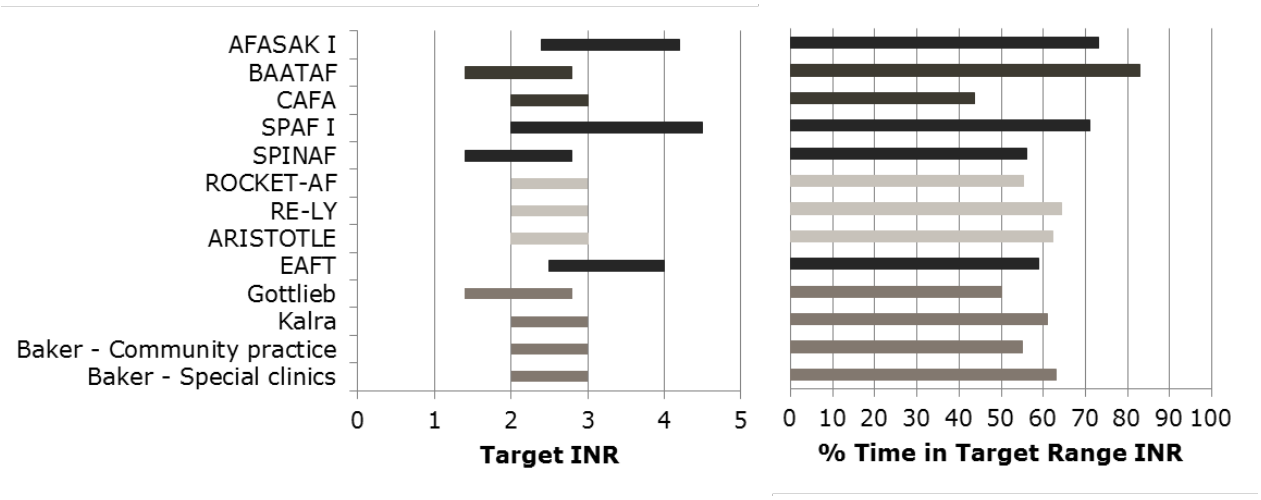


Figure 23: Target INR range and % Time in Target Range INR for newer randomised clinical trials (light grey), for actual practice (grey) studies and for older clinical trials (black)

3.9 Decision and communication of benefit-risk assessment

In order to communicate the benefit-risk assessment for warfarin to healthcare professionals, either the warfarin versus placebo or no treatment, or the warfarin versus new comparator would be meaningful. These 2 different assessments answer 2 different questions. The first one answers the question of whether to treat patients in non-valvular atrial fibrillation with warfarin or not, which is the situation physicians have been experiencing until recently. The second one answers whether there is any incremental benefit, and how large that benefit may be, for

choosing a newer anticoagulant compared to warfarin. In this case, the data presented in figure 17 - figure 19 may be helpful in establishing that warfarin and new anticoagulants are comparable, on fields where similar data exist. However, there are some fields where data are not available. These include "inconvenience" aspects of a treatment, such as issues with drug-drug and drug-food interactions and the need for regular INR monitoring with warfarin, and concerns over the lack of antidote and the lack of monitoring with the newer anticoagulants. However if any quantification of data and of preferences on this criteria had been available, they would likely have all pointed towards an advantage of newer comparators versus warfarin.

In order to communicate the benefit-risk assessment for warfarin to patients however, the requirements are different. Patients who want this level of information will need to understand the risks of adverse events if they are not treated at all, and the risks of adverse events under treatment. The communication of benefit-risk to patients for older products is complicated by the lack of availability of relevant data. However, this study demonstrates that visual displays such as that in figure 20 may be used to aid the communication to patients. Patient's disutility for softer criteria such as inconvenience is more difficult to quantify. Additionally, there may be an asymmetric aversion to risk (one for haemorrhagic, the other for ischemic stroke). It is important to avoid inconsistencies among conclusions of identical decision problems, but framed differently. For this, it might be helpful reasoning in terms of health metrics, like mortality and disability, rather than focusing on the cause of fatal or disabling events.

3.10 Discussion

In work stream 2 (WS2) a qualitative assessment of warfarin versus active comparators was done. The data used in the assessment came from 3 large RCTs. As for WS2 data availability was limited to published data, which influenced the definition of benefit and risk criteria. The benefit-risk criteria was chosen to mimic the criteria from WS1, however it was not possible to extract data on ischaemic stroke, and therefore the assessment was based on the criteria disabling stroke (ischaemic and haemorrhagic) and non-disabling stroke (ischaemic and haemorrhagic) the criteria major bleed was defined differently in the three assessments. For dabigatran and rivaroxaban major bleeds included intracranial haemorrhage (also included in the stroke criteria) but not fatal events. For apixaban major bleed excluded intracranial haemorrhage but included fatal events (also included in the 'all-cause mortality' criteria). Therefore the assessments in WS2 introduced a risk of double counting. The data from the warfarin arm of the newer RCTs was compared to data from the warfarin arm of the old RCTs in order to assess whether the evidence from the old and quite small RCTs matched the evidence from the new RCTs. There is a good agreement between the evidence from the older and newer RCTs, on the four criteria 'all-cause mortality', 'ischaemic stroke (fatal and non-fatal)', 'intercranial haemorrhage' and extracranial haemorrhage' despite the differences between the old and the new RCT in relation to target INR which is generally narrower in the new trials and TTR which is general lower in the never RCTs compared to the older.

4 Section 4: Individual benefit risk assessments for warfarin using patient level data

4.1 Introduction

There is limited evidence on how the benefit-risk profile for warfarin varies with individual patient characteristics and how to best identify those patients where the benefits of warfarin in reducing the risks of ischaemic events outweigh the adverse haemorrhagic effects. Most epidemiological research focuses on the estimation of relative measures (such as relative rates or odds ratios) rather than absolute risks and is based on population level analyses. But relative rates do not convey the absolute effect of treatment (32) and population level analyses may be inappropriate for an individual patient. Attributable risks are the probability of the occurrence of a particular event over a specific time-period as a result of exposure. Attributable risks (or risk difference), rather than relative rates, are of key importance in the assessment of the risk and benefit of drug therapies. An adverse event with a large relative rate that occurs only rarely may be less important than an event with a small relative rate occurring frequently.

In WS3, we use real life data from the CPRD database to estimate as accurately as possible the individual risks of bleeding and stroke in patients with atrial fibrillation (AF) treated with warfarin. Furthermore we explore characteristics that influence the individual benefit-risk balance.

4.2 Methods

4.2.1 Data source

Data for this study were obtained from the Clinical Practice Research Datalink (CPRD). CPRD collates the computerized medical records of general practitioners (GPs). GPs play a key role in the UK healthcare system, as they are responsible for primary healthcare and specialist referrals. Patients are semi-permanently affiliated with a practice that centralizes the medical information from the GPs, specialist referrals, and hospitalizations. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes [www.cprd.com]. Several software packages are used by GPs for their patients' medical records, including Vision from In Practice Systems Ltd and EMIS that combined covers just over 80% of all UK practices. The CPRD currently contains the complete anonymised patient medical records from GPs who use the system from In Practice Systems and who agree to adhere to "Recording Guidelines" that are subject to detailed quality control checks of data at both practice and individual patient level.

CPRD can now be linked individually and anonymously to other NHS datasets in England. Currently, over 325 GP practices in England are participating in this linkage (about 50% of CPRD). Participating GP practices send information on patient identifiers (including NHS number) and the anonymous CPRD patient number to a trusted third party. The linked database also sends information on patient identifiers and their patient numbers to the trusted third party. After matching, the patient identifiers are removed and CPRD is then linked anonymously to other databases.

Data from the following datasets were used for this study in addition to CPRD:

- Hospital Episode Statistics (HES). The HES includes records of inpatient hospitalisations (including date of admission and discharge, diagnoses and procedures)

4.2.2 Study design

The study design was a retrospective cohort. The start of follow-up was 1st January 1990, the start date of CPRD or HES data collection for each patient, whichever date came last. The end of follow-up was the end date of data collection for each patient in CPRD or HES, whichever date came earliest. Patients were censored 6 months after the date of the last warfarin prescription.

4.2.3 Study population

The cohort of warfarin users included patients aged ≥18 years with a documented record of AF. The index date was the first warfarin prescription issued at least 12 months after start of data collection. Patients with a record of rheumatic valve disease or patients with valvular repair/replacement were excluded.

4.2.4 Outcomes

The following outcomes were measured in this study.

On the benefit side:

- Ischaemic stroke (recorded in HES)
- Transient ischaemic attack (recorded in CPRD)

On the risk side:

- Haemorrhagic stroke (recorded in HES)
- Major bleed (recorded in HES). Major bleed was defined as symptomatic bleeding in a critical area or organ (excluding intracranial), such as intraspinal, intraocular, retroperitoneal, gastrointestinal, intraarticular or pericardial, or intramuscular with compartment syndrome.

4.2.5 Individual benefit-risk balance

We used methods described previously by the CPRD-group to calculate attributable risk and benefit for each individual (33). The first step was to estimate the cumulative incidence (CI) of an event for each set of patient characteristics using the survivor function in the Cox-proportional hazard regression model. In this way the model allows calculation of an individual's probability of an outcome. The second step is to obtain an estimate on the likely effects on this event of the drug. We assumed for this case study that the relative rate (RR) found in randomized clinical trials is an unbiased estimate of the drug effect and is expected to be consistent across the population. If the RR of drug effect is known, the underlying (unexposed) event probability can be estimated by dividing the event probability in the exposed through the RR. The attributable risk is the difference between the exposed and unexposed event probabilities (see text box 1 for schematic representation). The information on the RR's (drug effect) were obtained from the Cochrane meta-analysis and a meta-regression based on the literature review done in work stream 1 (18). The meta-regression was done to correct for differences in INR time in therapeutic range (TTR). Table 16 gives an overview of the selected RR's.

Table 15: Chosen relative rates for the different outcomes and their sources.

Outcome	Relative Rate	Source
TIA	0.45	Cochrane meta-analysis
Ischaemic stroke	0.28	WS1 – meta-regression
Haemorrhagic stroke	2.38	Cochrane meta-analysis
Major Bleed	1.23	WS1 – meta-regression

Texbox 1

RR = Cum Inc exposed/ Cum Inc unexposed
RR: from literature review
Cum Inc exposed: estimated in database with Cox proportional hazard model
Attributable risks/benefit = Cum Inc exposed – Cum Inc unexposed

The number of cases of haemorrhagic stroke and major bleed that would occur and the number of cases of ischaemic stroke and TIA that were prevented whilst exposed to warfarin were calculated by taking the average difference between cumulative incidence exposed and cumulative incidence unexposed per 1000 patients. The results were stratified for a patients risk for ischaemic stroke according to the CHA2DS2-VASc (consisting of: congestive heart failure, hypertension, age >75, diabetes mellitus, stroke, vascular disease, age 65-74 and female gender) and risk of bleed according to the HAS-BLED (consisting of: hypertension, abnormal liver/kidney function, stroke, bleed, labile INR, age>65, drugs/alcohol intake). The net benefit was calculated as the weighted sum of the probability of a beneficial outcome (in %) minus the probability of an adverse event (in %) caused by warfarin (attributable risk/benefit). The weight was chosen on the basis of the 1-year mortality of the outcome compared to the mortality of ischaemic stroke. This led to the following formula:

Net benefit = (Prevention of ischaemic stroke + Prevention of TIA*0.84) – (Occurrence of Haemorrhagic stroke*1.7 – Occurrence of Major bleed*0.91)

For each individual the net benefit was calculated. The net benefit represents the net probability (%) of the prevention of an ischaemic stroke. Then each patient was assigned to one of the following groups: unfavourable (net benefit < 0.5%), favourable (net benefit 0.5-1.5%) and a very favourable (net benefit >1.5%) benefit-risk balance. These limits were chosen on the basis of the variation and occurrence of the values of net benefit across the population, in order to create three comparable groups. Table16 shows the ranges of the quartiles.

Table 16: Range of quantiles of net benefit

Quantile	Estimate
100%	1675.7
99%	10.1
95%	4.2
90%	2.5
75% Q3	1.5
50% Median	1.0
25% Q1	0.6
10%	0.2
5%	-0.7
1%	-11.8
0% Min	-404.5

Patients that had a net benefit around average were considered to be favourable, patients that were below or above this average range were considered to be respectively unfavourable or very favourable. We used logistic regression

to find characteristics that were associated with having a unfavourable net benefit, because for these patients warfarin treatment is not necessarily the best choice.

4.3 Results

The study cohort consisted of 33,772 patients with AF exposed to warfarin. Baseline characteristics are shown in table 16. The mean age was 74.5(SD 11.3) and 18.3% of the patients were classified as being at high and 59.5% as being at low risk for ischaemic stroke according to the CHA2DS2-VASc score.

Table 15: Baseline characteristics

Characteristic	Category	Warfarin-users N	N=33772 %
Gender (male)	Male	17485	51.8
Age	<65	5923	17.5
	65-74	9053	26.8
	75-84	12611	37.3
	>85	6185	18.3
Social economic status	20% (most deprived)	7559	22.4
	21-40%	8614	25.5
	41-60%	7061	20.9
	61-80%	6011	17.8
	81-100% (least deprived)	4527	13.4
Smoking status	Current smoker	23907	70.8
	Non-smoker	4609	13.6
	Ex-smoker	3569	10.6
	Unknown	1687	5.0
Body mass index (kg/m^2)	Underweight (<20)	1138	3.4
	Normal (20-<25)	7970	23.6
	Overweight (25-<30)	11974	35.5
	Obese (≥30)	8612	25.5
	Unknown	4078	12.1
CHA2DS2-VASc	High	6172	18.3
	Moderate	7497	22.2
	Low	20103	59.5
HAS-BLED	High	3192	9.5
	Moderate	3351	9.9
	Low	27229	80.6
Prescribing in the 6 months before index date			
	Antiplatelets	14673	43.4
	Antidepressants	3266	9.7
	Antidiabetics	2183	6.5
	NSAIDS (excl. aspirin)	5743	17.0
	Corticosteroids (rectal or oral)	2699	8.0

	Hypnotics	2768	8.2
	Medicines that have interactions with warfarin	20473	60.6
Diagnoses ever before index date			
	Liver failure	179	0.5
	Anemia	22423	66.4
	Congestive heart failure	1298	3.8
	Coronary heart disease	4899	14.5
	Diabetes mellitus	9362	27.7
	Alcohol and drug abuse	4088	12.1
	Falls	744	2.2
	Hypercholesterolemia	3741	11.1
	Hypertension	5083	15.1
	Major bleed	16170	47.9
	Cancer	1861	5.5
	Minor bleed	8473	25.1
	Proteinuria	4361	12.9
	Renal insufficiency	348	1.0
	Stroke ischaemic	792	2.3
	Stroke haemorhagic	29167	86.4
	Stroke unspecificed	898	2.7
	Thrombocytopenia	129	0.4
	TIA	2308	6.8
	Vascular disease	110	0.3
	Deep Venous Thrombosis	2706	8.0
	Pulmonary embolism	4220	12.5

Table 17 shows the number of prevented ischaemic strokes, transient ischaemic attacks, and number of excess cases of haemorrhagic stroke and major bleed stratified by the risk for stroke (according to CHA2DS2-VASc) and bleeding (according to HAS-BLED) per 1000 patients. Also the net benefit (the net number of prevented ischaemic strokes) are shown per risk group. Patients with both a high risk for stroke and bleed have a net benefit of +85 cases of ischaemic stroke prevented per 1000 patients. Those who have a low risk for stroke and bleed have a net benefit of +15 cases of ischaemic stroke prevented per 1000 patients. In table 18 the results are shown only for baseline risk of stroke.

Table 16: Potential number of prevented ischaemic strokes, transient ischaemic attacks, and number of excess cases of haemorrhagic stroke, major bleed stratified by baseline risk for stroke (according to CHA2DS2-VASc) and bleeding (according to HAS-BLED)

		Benefits (no. of cases prevented per 1000 patients)		Risks (excess no. of cases per 1000 patients)		
Baseline risk stroke (CHA2DS2-VASc)	Baseline risk bleed (HAS-BLED)	Ischaemic stroke (reported in HES)	Transient ischaemic attack (reported in CPRD)	Haemorrhagic stroke (reported in HES)	Major bleed (reported in HES)	**Benefit - Harm**
High	High	112	47	10	54	**+85**
Moderate	High	119	46	20	46	**+82**

Low	High	78	0	0	78	**+7**
High	Moderate	93	57	14	52	**+70**
Moderate	Moderate	66	45	9	50	**+43**
Low	Moderate	73	33	8	54	**+38**
High	Low	71	28	8	63	**+24**
Moderate	Low	52	24	8	55	**+8**
Low	Low	46	27	8	45	**+15**

*Events were weight by their 1-year mortality compared to ischaemic stroke; transient ischaemic attack (0.84), haemorrhagic stroke (1.70), major bleed (0.91)

Table 17: Potential number of prevented ischaemic strokes, transient ischaemic attacks, and number of excess cases of haemorrhagic stroke, major bleed stratified by baseline risk for stroke (according to CHA2DS2-VASc).

	Benefits (no. of cases prevented per 1000 patients)		Risks (excess no. of cases per 1000 patients)		
Baseline risk stroke (CHA2DS2-VASc)	Ischaemic stroke (reported in HES)	Transient ischaemic attack (reported in CPRD)	Haemorrhagic stroke (reported in HES)	Major bleed (reported in HES)	**Benefit - Harm**
High	95	43	10	57	**+63**
Moderate	56	28	8	53	**+17**
Low	47	27	8	45	**+16**

*Events were weight by their 1-year mortality compared to ischaemic stroke; transient ischaemic attack (0.84), haemorrhagic stroke (1.70), major bleed (0.91)

In figure 24-28 plots are shown in which the attributable benefit is given on the y-axes and the attributable risk is given on the x-axes. In each plot different outcomes are chosen to represent benefit or risk. Each patient is represented by a dot. Patients that appear more in the lower right corner have more risk than benefit, whilst patients that appear in the upper left corner have more benefit than risk. Figure 24 shows a plot for the total attributable benefit (prevention of ischaemic stroke and TIA) and the total attributable risks (haemorrhagic stroke and major bleed) per patient for a sample of 10.000 patients. In the figure 25 and figure 26 the attributable risk for having respectively a haemorrhagic stroke or a major bleed were plotted against the attributable benefit for prevention of ischaemic stroke. Figure 27 and figure 28 show the similar plots for the outcomes haemorrhagic stroke and ischaemic stroke but stratified for patients with a high and low score for the CHA2DS2-VASc and HASBLED score.

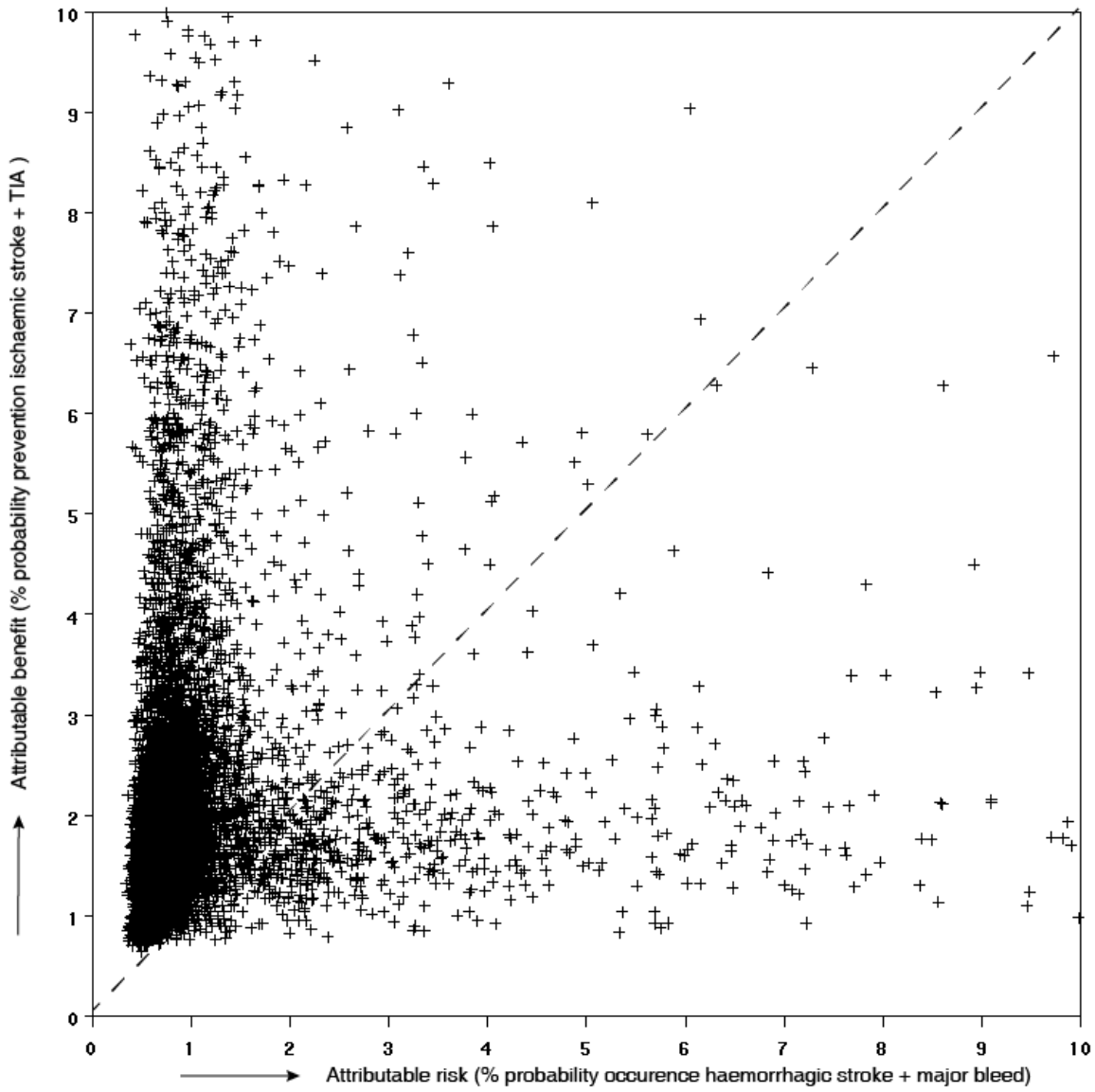


Figure 24 : Potential risk (occurrence of haemorrhagic stroke + major bleed) versus potential benefit (prevention of ischaemic stroke + TIA) in 4 years for each individual patient with atrial fibrillation due to the treatment with warfarin (sample of 10.000 patients).

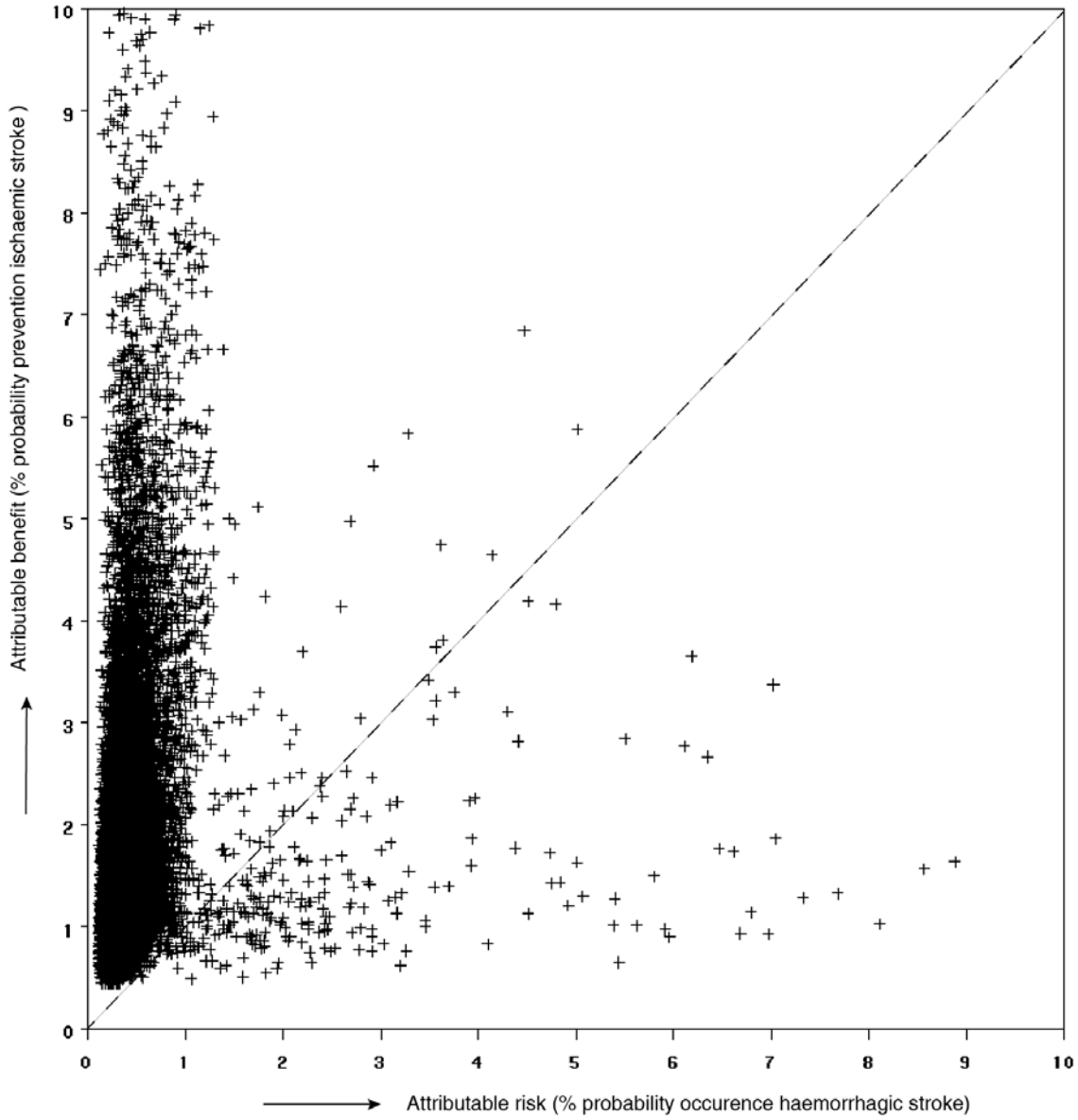


Figure 25: Potential risk (occurrence of haemorrhagic stroke) versus potential benefit (prevention of ischaemic stroke) in 4 years for each individual patient with atrial fibrillation due to the treatment with warfarin.

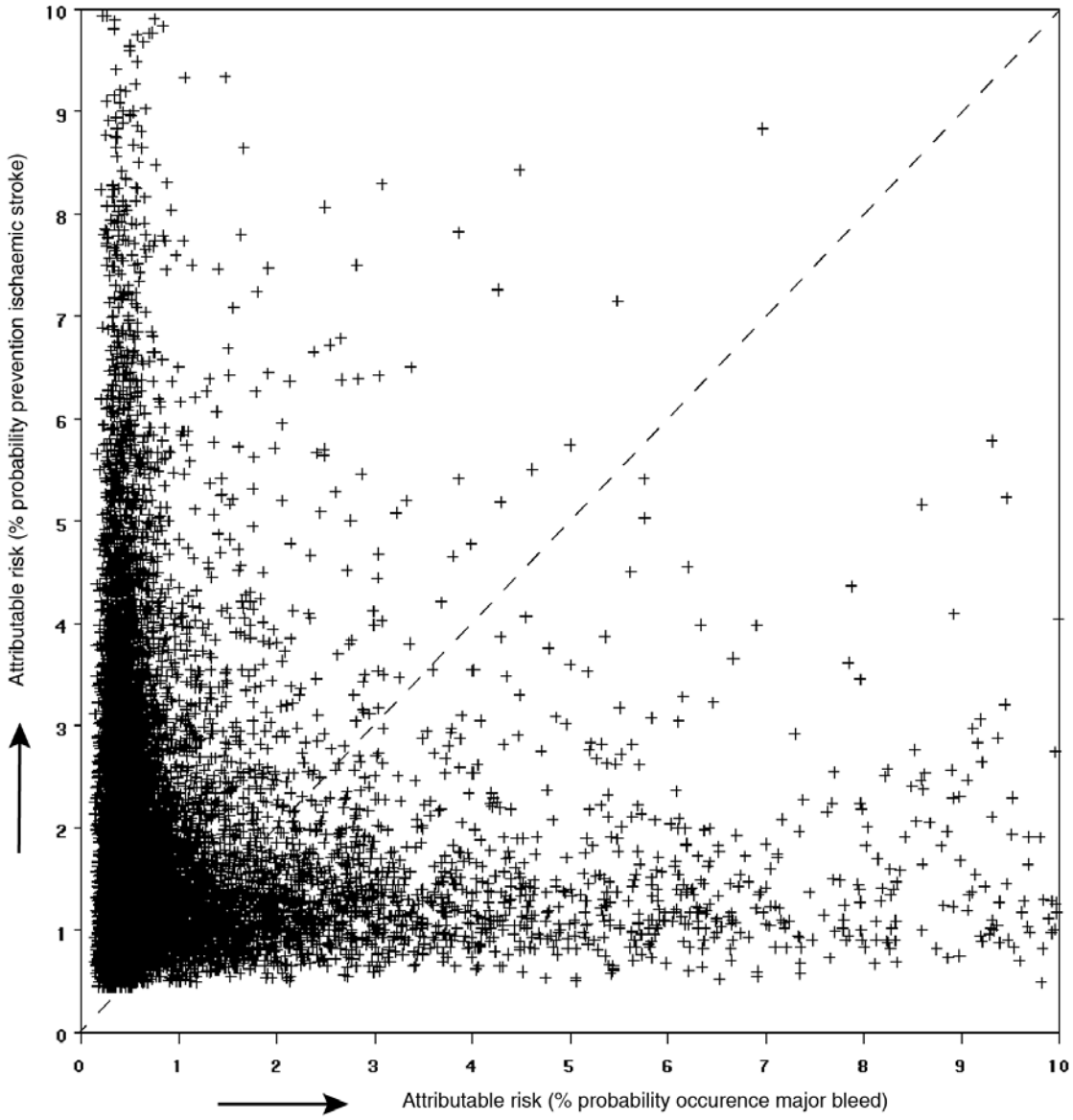


Figure 26: Potential risk (occurrence of major bleed) versus potential benefit (prevention of ischaemic stroke) in 4 years for each individual patient with atrial fibrillation due to the treatment with warfarin.

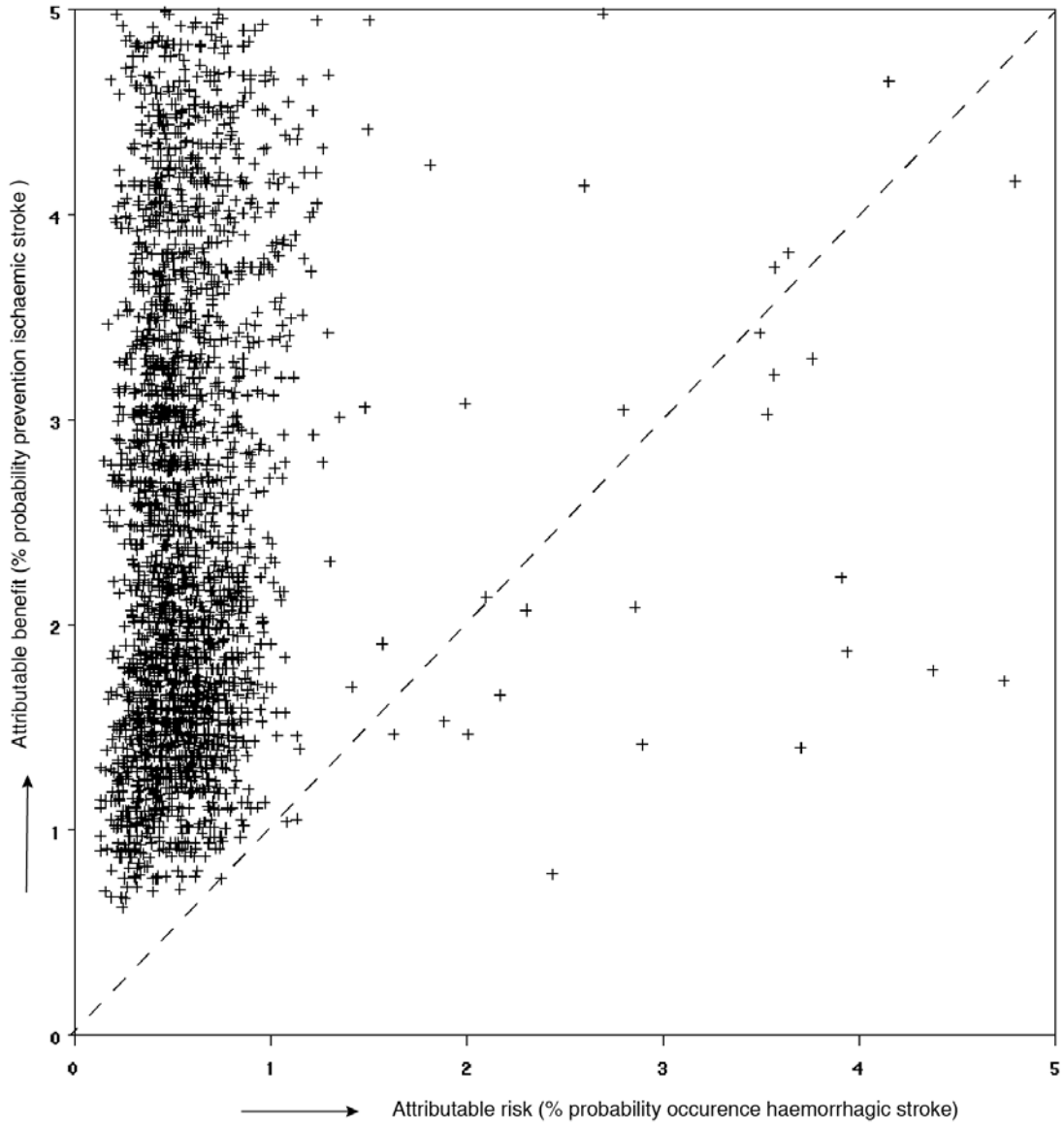


Figure 27: Potential risk (occurrence of haemorrhagic stroke) versus potential benefit (prevention of ischaemic stroke) due to the treatment with warfarin in 4 years for each individual patient with atrial fibrillation having a high risk of stroke (CHADSVASC ≥ 2) and high risk of bleed (HASBLED ≥ 2)

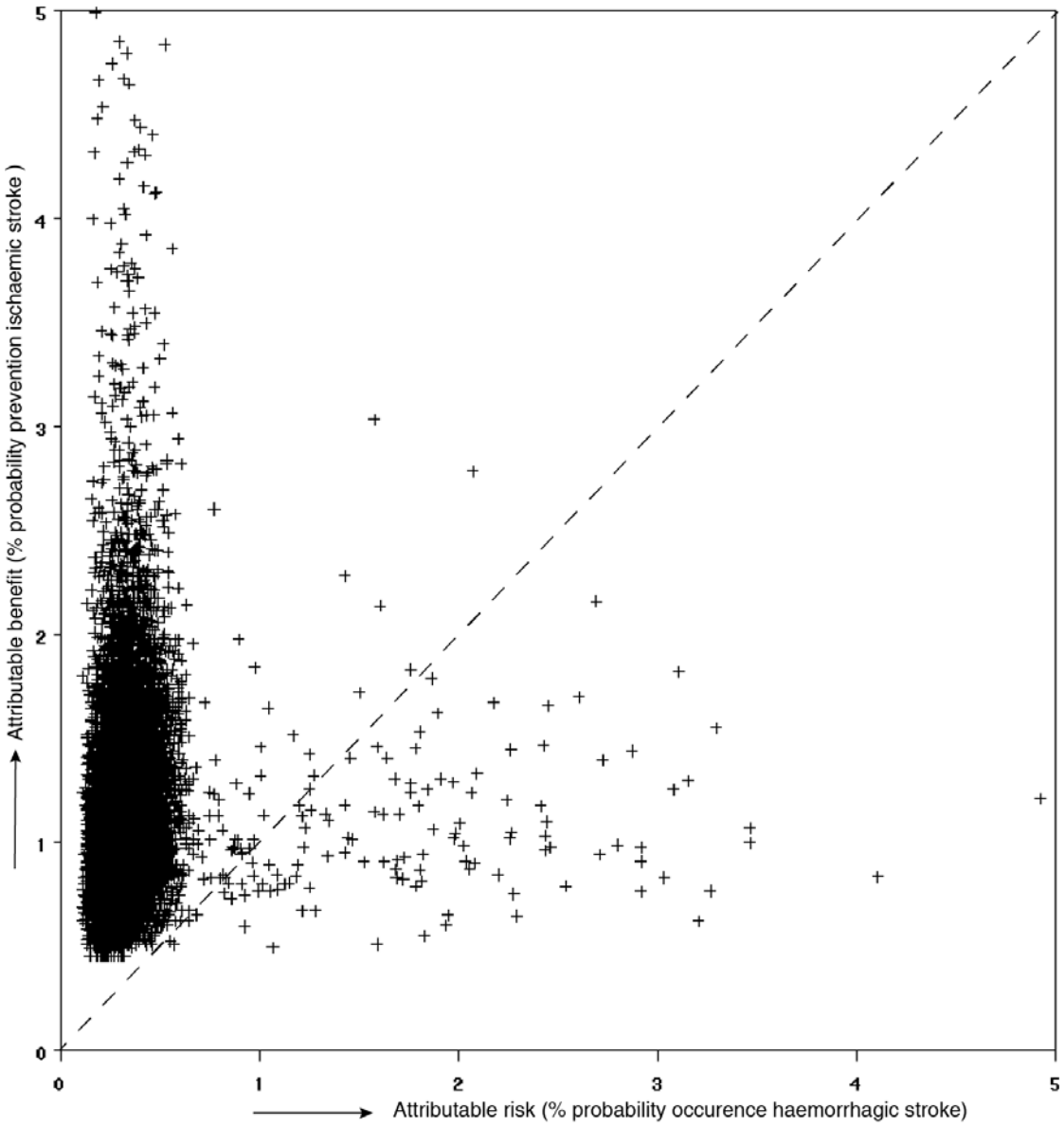


Figure 28: Potential risk (occurrence of haemorrhagic stroke) versus potential benefit (prevention of ischaemic stroke) due to the treatment with warfarin in 4 years for each individual patient with atrial fibrillation having a low risk of stroke (CHADSVASC ≥ 2) and low risk of bleed (HASBLED ≥ 2)

The mean net benefit among patients was 1.17% (SD 16.0%) ischaemic stroke cases or equivalent prevented. A total of 7036 (20.8%) patients were classified as having a unfavourable benefit-risk balance and 7950 (23.54%) as having a very favourable benefit-risk balance. The rest of the patients had a favourable net benefit. Table 18lists the characteristics that were significantly associated with a unfavourable benefit-risk balance. Conditions that increased the risk of having an unfavourable benefit-risk balance were congestive heart failure (OR 2.67, 2.27-3.14), cancer (OR 2.51, 2.19-2.88), minor bleed (OR 2.68, 2.25-3.18) and renal insufficiency (OR 3.30, 2.37-4.60). Coronary heart disease (OR 0.53, 95% CI 0.45-0.61), hypertension (OR 0.41, 95% CI 0.36-0.46), previous ischaemic stroke (OR 0.20, 95% CI 0.12-0.33) and vascular disease (OR 0.16, 95% CI 0.43-0.64) were predictors for a more favourable benefit and are listed in table 19.

Table 18: Characteristics associated with a less favourable (<0.5) net benefit.

Characteristic		Odds ratio (95% CI)	Unfavourable	Very favourable
Prescriptions (6 months before index date)				
Antiplatelet agents	No	Reference	4013 (50.8)	3886 (49.2)
	Yes	1.38 (1.21-1.57)	3937 (55.6)	3150 (44.5)
Anti-diabetic drugs	No	Reference	6747 (49.11)	6991 (50.9)
	Yes	1.70 (1.25-2.30)	289 (23.16)	959 (76.8)
Corticosteroids	No	Reference	6220 (45.7)	7397 (54.3)
	Yes	1.99 (1.60-2.46)	816 (59.6)	553 (40.4)
Hypnotics	No	Reference	6522 (48.2)	7011 (51.8)
	Yes	0.68 (0.57-0.83)	514 (35.4)	939 (64.6)
NSAID's	No	Reference	6063 (50.0)	6064 (50.0)
	Yes	0.27 (0.23-0.31)	973 (34.0)	1886 (66.0)
Medicines that have interactions with warfarin*	No	Reference	2393 (46.7)	2735 (53.3)
	Yes	1.32 (1.16-1.52)	4643 (47.1)	5215 (52.9)
Comorbidities (ever before index date)				
Anaemia	No	Reference	6828 (47.9)	7428 (52.1)
	Yes	0.30 (0.22-0.40)	208 (28.5)	522 (71.5)
Congestive heart failure	No	Reference	5713 (46.2)	6666(53.9)
	Yes	2.67 (2.27-3.14)	1323 (50.8)	1284 (49.3)
Coronary heart disease	No	Reference	5427 (54.5)	4538 (45.5)
	Yes	0.52 (0.45-0.61)	1609 (32.1)	3412 (68.0)
Diabetes Mellitus	No	Reference	6585 (52.1)	6066 (48.0)
	Yes	0.06 (0.05-0.06)	451 (19.3)	1884 (80.7)
Falls	No	Reference	5930 (45.8)	7029 (54.2)
	Yes	2.14 (1.79-2.57)	1106 (54.6)	921 (45.4)
Hypertension	No	Reference	3746 (53.5)	3250 (46.5)
	Yes	0.41 (0.36-0.46)	3290 (41.2)	4700 (58.8)
Ischaemic stroke	No	Reference	6988 (48.4)	7451 (51.6)
	Yes	0.20 (0.12-0.33)	48 (8.78)	499 (91.22)
Cancer	No	Reference	4526 (42.3)	6172 (57.7)

	Yes	2.51 (2.19-2.88)	2510 (58.5)	1778 (41.5)
Minor bleed	No	Reference	5739 (45.0)	7014 (55.0)
	Yes	2.68 (2.19-2.88)	1297 (58.1)	936 (41.9)
Renal insufficiency	No	Reference	6766 (46.7)	7729 (53.3)
	Yes	3.30 (2.37-4.60)	270 (55.0)	221 (45.0)
TIA	No	Reference	6617 (49.5)	6739 (50.5)
	Yes	0.52 (0.43-0.64)	419 (25.7)	1211 (74.3)
Vascular disease	No	Reference	6534 (52.9)	5829 (47.2)
	Yes	0.16 (0.13-0.19)	502 (19.1)	2121 (80.9)

Table 19 shows the actual numbers of warfarin users identified within CPRD in different categories of favourability; from the most favourable category in which a patient has the benefits, but not the adverse events to the patients who do not have the benefits, but do have the adverse events.

Table 19: Absolute number of events in warfarin users in different categories of favourability

		No Haemorrhagic Stroke		Haemorrhagic Stroke	
		No Major Bleed	Major Bleed	No Major Bleed	Major Bleed
No Ischemic Stroke	No TIA	23563	1235	209	11
	TIA	323	33	7	1
Ischemic Stroke	No TIA	296	35	14	1
	TIA	31	4	1	0

4.4 Conclusion

We confirmed that the net benefit of warfarin for the overall AF population is positive. However, there is a large variation of benefit-risk balance across this population and some patients have a unfavourable net benefit than others. Patients with history of several chronic conditions have a higher risk of having less benefit from treatment than the average patient. Cancer and renal failure for example, are associated with coagulation disorders and this may suggest an increased risk of bleeding and a unfavourable net-benefit. However, patients with comorbidities that are known risk factors for the occurrence of ischaemic stroke seem to benefit more from warfarin treatment. Only a small proportion of patients (around 5%) have a negative net benefit. For these patients, warfarin should not be advised. In further research, these patients should be characterised more specifically.

4.5 Discussion

The current method tries to capture characteristics that determine an individuals' benefit-risk balance for warfarin rather than a population benefit-risk balance. The use of population means alone in decision modelling does not give the possibility to capture variability in the risk-benefit profile across a population. The risks and benefit may not be evenly distributed across a population. Risks may occur more frequently in specific subpopulations whilst others benefit more from therapy. With this method we are able to identify which patients might have a more or less

favourable benefit-risk balance than others. There will always be individual patients for whom, when actually treated, the risks outweighs the benefits, but in general for each combination of baseline risk levels this was not the case.

There is a substantial group that has a unfavourable net benefit, which means that their net benefit is marginal or even negative (<0.5 %) and they will benefit less from treatment than the average patient that is on warfarin. For these individuals warfarin might not be the best treatment option. By identifying these patients we could assist a physician to decide between treatment options.

With any medicinal compound there are a balance of benefits and risks to be made for each individual when deciding whether to take it (or be prescribed it, or for it to be licensed, depending on whose decision is being considered). The ideal compound would provide the maximum favourable effect but without unfavourable effects to the majority of patients. There would be some people who experienced any unfavourable effects, and from a pharmacological perspective it is also assumed that these would be the same people who experienced the favourable effects. It is also to some extent assumed that those who do not experience the favourable effects tend to not also suffer from the unfavourable effects. Ideally there should be very few people who fail to reap the benefits but suffer the risks. Data on this scenario, either in trials or observational studies, is almost always lacking and assumptions have to be made. This overall balance helps answer the question of which patients could take this drug.

Table 19 demonstrates that warfarin does indeed behave like this, providing additional reassurance that the overall balance of benefits and risks is positive. However the aim for any treating physician may well be to try and treat those who fall into the top left hand side of the table, and avoid treating those who fall into the bottom right, especially when suitable alternatives are available. Identifying the factors that predict where any individual patient may lie is key to this decision. It helps answer the question whether this drug is right for the individual patient. The fortuitous consequence of such an approach if one can successfully identify such individuals is that the overall balance of benefits and risks in the population 'in reality' improves as well.

In this report we have shown how we can use clinical trial data to make trade-offs between benefits and risks even for older drugs where good quality data may be lacking. In benefit-risk assessment it is of key importance that the data that are used are representative for the population that uses the medicine. Whilst experimental data from clinical trials provide the effects of a treatment in perfect conditions (efficacy), the evidence from observational data can provide the effects in real life (effectiveness). This difference in benefit-risk has been described in literature as the efficacy-effectiveness gap (34). Similar considerations are true for the safety data from clinical studies, as the exclusion criteria, study monitoring and the study populations may lead to lower overall adverse event rates and severity than will be observed in the wider population. Within RCTs the variability in the study population is expected to be minimised with the aim of enhancing the signal-to-noise ratio and increasing the power of the study. This may involve trial staff making a special effort to convince patients to take the trial medications according to the prescribed dosing regimen to maximise efficacy, and narrow selection criteria to eliminate those with a low susceptibility for toxicity, e.g. those with co-morbidities. However, in real life such dedicated trial support will not be available, and prescriptions will be given to those outside the trial population, and thus variability will increase which may lead to a shift in the overall benefit-risk profile in ‘reality’ as opposed to the ‘expectation’ of it. In this case study the benefit-risk profile does not shift on a population level, but it does show that it differs for specific individuals. It advocates for the treatment to be more tailored to the individual.

Sources of variability are differences in genotype, presence of comorbidities, adherence to treatment and off label prescribing. Furthermore, it has been shown that the usage of drugs in actual clinical practice is different than in a clinical trial setting. For example in clinical trials with COX-2 inhibitors, the usage was restricted to patients with rheumatoid arthritis or osteoarthritis that used these medicines in high dosages for prolonged time. However, in actual clinical practice patients often used these medicines intermittently and at lower dosages and didn't have an indication of rheumatoid arthritis or osteoarthritis. Consequently, this will change the benefit risk balance. The question then arises whether one should lower the expectations of the benefit-risk balance to the level of reality, by assessing the benefit risk balance based on real-world data, or try and raise reality up to the level of expectations through effective Risk Management measures, or a combination of the two (34).

Although we have a clear overview of the benefit-risk profile through experience, the new Pharmacovigilance legislation now requires the periodic evaluation of both benefits and risks of a medicine with more level of detail. Whilst regulators have a desire for an armamentarium of drugs with an acceptable balance of benefits and risks, for the individual patient or prescribing physician, alternatives emerging on to the market may require a re-evaluation of prescribing choice. With the availability of electronic healthcare data we are able to quantify the actual rate of the beneficial outcomes for those treated with warfarin in the real world as compared with the idealised clinical trial setting.

A limitation of this study was the discrimination between haemorrhagic stroke and ischaemic stroke in CPRD is limited as frequently non-specific codes are used. However, it may be possible to improve this discrimination using HES data, because data are recorded more frequently by aetiology (haemorrhagic or ischaemic stroke). Although the use of this linkage improves the recording of the type of stroke, still 26% of the strokes are classified as being 'unspecified'. Although this is likely to reflect a medical situation, in the follow up of this project multiple imputation techniques will be used to classify the type of stroke. It is also not possible to distinguish in CPRD between paroxysmal, persistent and permanent AF due to non-specific AF coding. The assumption that the relative rate as seen in clinical trials is constant across the whole population is a strong one, especially considering the argument that real life use is more variable, which implies lower potential efficacy and higher potential for greater toxicity. Relaxing this assumption by assuming for example that the absolute effect as seen across trials is the same as in the whole population could result in different conclusions being drawn. However, the model can be easily adjusted if there would be strong evidence that RR's are different among subpopulations. This is the same for the weighing factor used to calculate the net benefit. In the current study we used mortality rate compared to the mortality rate of ischaemic stroke as a weighing factor, but also other weights, such as utility, can be justified.

Another limitation of this study is that we didn't take INR-control into account. Warfarin use requires frequent blood tests to monitor the level of anticoagulation which is measured by the International Normalised Ratio (INR). Previous reports have found lower risks of ischaemic stroke at INR levels between 2.0 and 3.5 and increasing risk of thromboembolic events with INR values below 2.0, and increasing risk of haemorrhages with INR values above 3.5 (35-37). Poor anticoagulation control occurs frequently in AF patients. It has been reported that most AF patients admitted to the hospital with an ischaemic stroke who were candidates for anticoagulation, were either not taking warfarin or had a sub therapeutic INR at the time of event (38). Moreover, several studies have found that the INR values were out of the target range approximately half the time (39). This poor anticoagulation control can be caused by several reasons including but not limited to adherence, drug-drug and drug-food interactions. Furthermore, intercurrent illness or an exacerbation of an existing illness may also contribute to changes in INR levels (40). Therefore, when assessing the benefit-risk balance of warfarin, it is of importance to take quality of anticoagulation control into account.

5 Section 5

5.1 Overall Discussion

This case study was carried out to identify whether there are specific challenges in conducting benefit-risk reviews for older products and also to incorporate individual benefit-risk modelling. The aim for the individual benefit-risk modelling was to demonstrate the diversity of benefit-risk balance across the population and to find characteristics that might be associated with having an unfavourable net benefit. This approach was possible because the case study group had access to individual patient data from CPRD. Warfarin was chosen for the case study because it is an older product that is widely used but has a complex safety profile.

There is some clinical trial data in the indication of non-valvular atrial fibrillation and also three relatively new studies in which standard of care (i.e. warfarin) was used as a comparator for new anticoagulants have been identified (28, 30, 31). These studies provide clinical trial data to current standards on warfarin as well as the new products and allow for the comparison of older clinical trial data to the new data as well as allowing a comparison of warfarin against newer anticoagulants.

The new studies suggested that the rate of events on warfarin in the older studies was similar to data collected under new clinical trial conditions. This suggests that our assessment of the benefit-risk of warfarin therapy versus no treatment for patients with non-valvular AF is robust, although clearly “no treatment” is a different option to placebo. However the information from the new clinical trials was essential in helping to understand the benefit-risk profile for warfarin, and to provide up-to-date visual comparisons that may help patients and health care professionals to decide between various treatment options with delicate benefit-risk balance. The availability of these data was due to newer products being submitted for marketing authorisation which will not always be the case for older products, in which case the results would be similar to those seen in work stream 1, i.e. based on extremely limited relevant data, with consequent uncertainty to the external validity and generalisability to more recent medical practice.

The limitations of the available data for older products affect the development of the value tree, which for practical reasons needs to be based on data that are available rather than allowing the value tree to be developed based on the application of formal criteria. This means that there may be clinical outcomes which are very relevant to a B-R assessment and for which no data or only limited or unusable data are available, for example post-marketing spontaneous reports. This may decrease the overall validity of a value tree with a potential bias towards more Benefit criteria and less Risk criteria (41). This results from eliminating some undesirable effects from the value tree just because there is no exploitable data (non-comparative, or no incidence, or limited epidemiology data etc.). Some of these undesirable effects would have played a major role in the BR assessment if data had been available (e.g. serious bleeding events). Within the benefit-risk assessment, there may be an asymmetric aversion to risk (for example different aversions to haemorrhagic, versus ischaemic stroke). As it is important to avoid inconsistencies among conclusions of identical decision problems, which are simply framed differently, it might be helpful reasoning in terms of health metrics, like mortality and disability, rather than focusing on the cause of fatal or disabling events.

The impact of missing data on the value tree and consequent benefit-risk decision may depend on the benefit-risk model used. For example, standard BRAT tools have difficulty with missing data or data which are not biostatistically acceptable. When aggregating data from different sources it is important to be aware of issues such as different definitions of outcomes and different way of measuring certain effects, and also issue of bias when combining data. This lead to some exercise of data transformation or even criteria customization in order to have matching criteria

across the sources of evidence. However, more qualitative use of the BRAT framework will allow the user to incorporate some degree of flexibility. For MCDA, this is less a problem as the model can accommodate all types and format of data. The building of the value tree then depends mainly on what is relevant for BR assessment and what is not (many secondary redundant efficacy criteria, many mild tolerable AEs etc.) (42).

Another general issue in the construction of value trees is that different parties constructing them may have different levels of access to the same information. For example there will always be more information in a clinical study report than in a summary public assessment report or a published paper. Additionally regulators may also be able to request further analyses and information from trial sponsors (for example different variables of interest, different methods for handling missing data) whereas those reviewing only published data cannot, again leading to an asymmetry of information. Therefore there is the potential that those with access to the fuller version of the data set may appear to make slightly different decisions from those that do not whereas these decisions are actually based on different amount of information. For older products, it may be that regulators have a lot of information in the periodic safety update reports that is not generally available for public use.

With the help of patient level data we were able to show that although the overall benefit risk balance for a product seems acceptable, it might be very different from one patient to another. Some patients might benefit more than others, while others might have more risks. In this case study we have tried to use methods to identify these patients. A person's benefit-risk balance may be influenced by the specific combination of other risk factors, or by the fact that the usage of a product in real life is very different from a clinical trial setting. By mapping this benefit-risk profile of a medicine we might help prescribing physicians in giving the right drug to the right patient. Advantage of this method is that it can be easily adapted to different scenarios by changing the input data such as the relative rates and the weights. Therefore this method can be applied for both older drugs as new drugs.

Warfarin has been used therapeutically for this indication for over 50 years. Consequently the studies on which the benefits were initially established are not of the same quality as those of newly-licensed medicines. The original clinical trial data for earlier warfarin trials may not even still be available. This is likely to be an issue for a number of products with long established use, and hampers formal benefit-risk assessments using standard methodologies and visualisation techniques.

Considering the need for interpretation by patients, simple visuals have been used in this report to allow a one-dimensional benefit-risk assessment, although this can be an important composite such as all-cause mortality. This may help in interpretation and discussion with patients about their treatment options, but may risk oversimplifying a benefit-risk problem.

Finally, warfarin is used for a wide range of indications requiring anticoagulation, and each of them carries their own benefit-risk balance. Therefore it is clear that the benefit-risk assessment should be conducted on a specific indication basis and should not be generalised to other indications not being considered in the decision model. However the linked decisions between different models and indications may be further explored to ensure the decisions are made consistently and transparently.

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7 Appendices

7.1 Appendix 1: WS1 Literature search Strategy

A thorough literature search was performed to identify previous conducted data synthesis on efficacy and safety for the use of warfarin in the indication of atrial fibrillation. The review will be limited to include previous systematic reviews and meta-analysis.

We will search the following electronic databases:

- Cochran Database of systematic reviews
- Cochran Database of Abstracts of Reviews of Effects (other reviews)
- Medline
- Scopus

The search will be performed using following terms:

- Warfarin, coumadin, jantoven, marevan, lawarin, waran or warfant
- Atrial fibrillation, atrium fibrillation, auricular fibrillation, heart fibrillation, cardiac fibrillation
- Systematic review, meta-analysis

Excluding

- Rivaroxaban, dabigatran, apixaban

The search will be limited by language English.

(The full search algorithms can be view under Search algorithm)

Reference lists of all relevant papers will be searched to identify other potentially relevant articles. The titles and abstract from the electronic search will be screened by the two work stream 1 participant Christine Hallgreen and Nan Wang, who will decide on inclusion or exclusion.

The search algorithm will be validated by its ability to identify following key publications either in the electronic search or in the references:

- Agarwal, S., Hachamovitch, R., & Menon, V. (Apr 2012). Current trial-associated outcomes with warfarin in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis. Arch Intern Med, 172(8), 623--31; discussion 631-3.
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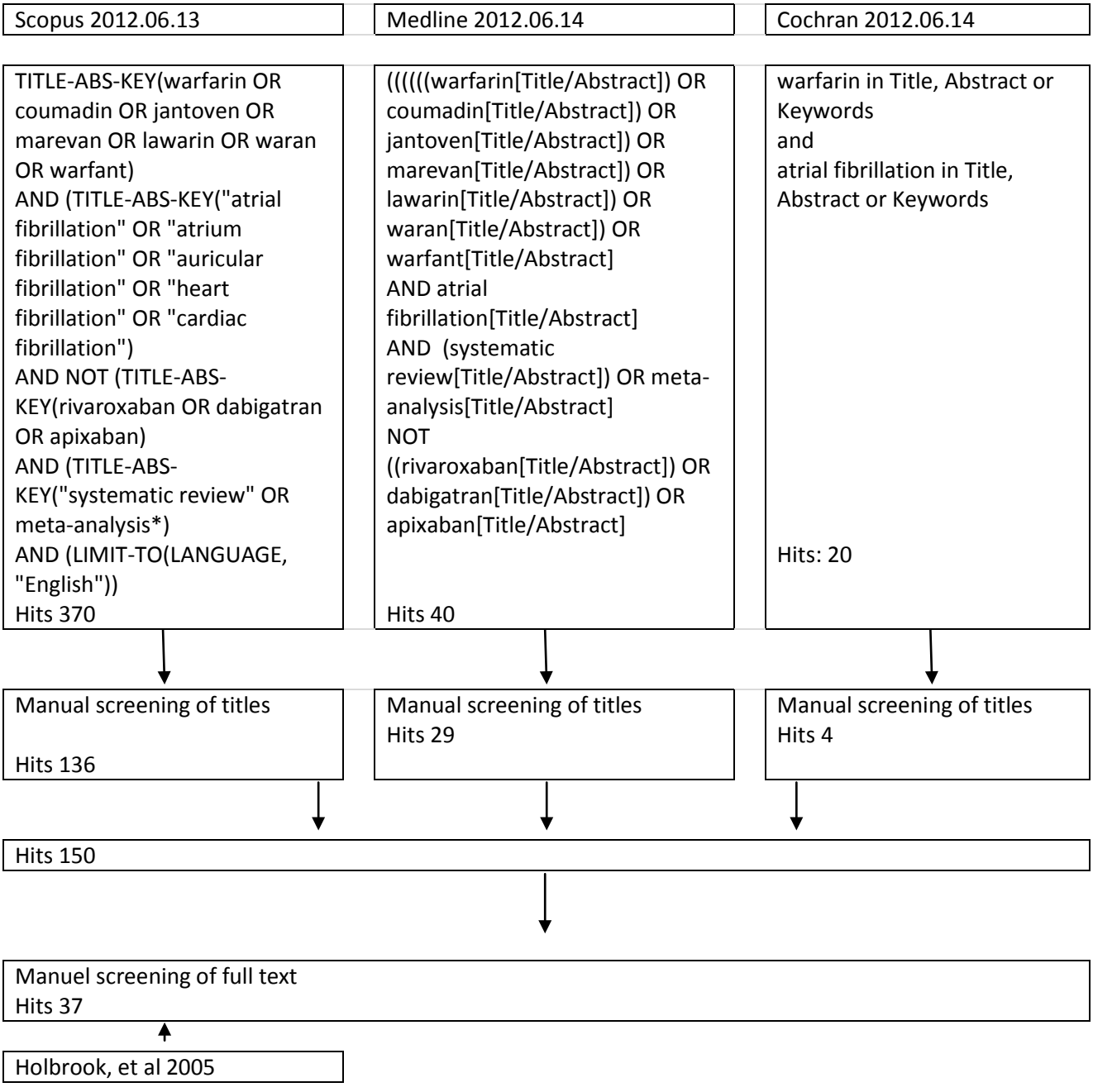
Review inclusion criteria

- The papers included in this review should include the data on
- Reduction in embolic stroke

- Reduction in disability
- Reduction in hospitalisation
- Reduction in death
- Haemorrhagic stroke
- Ophthalmic haemorrhage (possible leading to blindness)
- GI haemorrhage
- Drug-drug interactions
- Drug-food interactions
- Variability in INR

For the treatment of patients with non-valvular atrial fibrillation with warfarin compared to placebono treatment

7.1.1 Search algorithm



7.2 Appendix 2: Summary of randomised clinical trials

7.2.1 AFASAK

Randomised open label (The aspirin and placebo arms was double-blinded)
Computer-generated randomised
Randomised to 3 groups (warfarin, aspirin, placebo)
Primar storke prevention trial
Double-blind: aspirin vs. placebo
Open-lable: warfarin
On therapy analysis
Exclusion during the trial none
Loses to follow up: not reported
Off therapy:222 patients in the three groups
Follow-up 2 years

Inclusion criteria	Age 18 years or above ECG-Verified chronic AF
Exclusion	Previous anticoagulation therapy for more than 6 months Cerebrovascular events within the past month Contraindication for warfarin or aspirin Previous side-effects of warfarin or aspirin Current treatment with warfarin or aspirin Pregnancy or breast-feeding Persistent blood pressure above 180:100 mmHg Psychiatric diseases, including chronic alcoholism Heart surgery with valve replacement Sinus rhythm Rheumatic heart disease Refusal to participate
Arms	
Warfarin	Adjusted dose INR range 2.8-4.2
Aspirin	75 mg once daily
Placebo	

Patient characteristics

	Warfarin (n=335)		Aspirin (n=336)		Placebo (n=336)	
	Number	%	Number	%	Number	%
Male	176	53	184	55	180	54
Female	159	47	152	45	156	46
Previous TIA	4	1	5	1	6	2
Previous stroke	16	5	12	4	15	4
Previous AMI	27	8	23	7	27	8
Angina pectoris	63	19	54	16	54	16
Diabetes	25	7	26	8	33	10
History of hypertension	108	32	112	33	103	31
Smoking	133	40	124	37	117	35
Heart failure	168	50	183	54	170	51
Thyrotoxicosis	16	5	12	4	13	4

Reference (12, 18)

7.2.2 CAFA

Randomised double-blinded placebo-controlled
Randomisation by sequential use of packages with warfarin or placebo according to a predetermined random order.
Randomised to 2 groups; warfarin vs. placebo
Primary stroke prevention trial
Exclusions: 2 patients on warfarin and 3 on placebo
Losses to follow up where not reported
Off therapy: 49 in warfarin group an d43 in placebo group
Triple blinded (patient, co-ordinating center, and investigators)
Efficacy analysis was used for primary analysis and intention to treat for secondary analysis
The trial was terminated when the results of AFASAK, SPAF I, and BAATAF were know, without analysis of interim results, with a mean follow-up of 1.3 years

Inclusion	Chronic atrial fibrillation documented to be present for one month or more or paroxysmal atrial fibrillation occurring at least three times in the previous 3 months (documented at least twice on the ECG) Age 19 years or older Absence of any mitral valve stenosis on two-dimensional echocardiography Requirement for anticoagulation
Exclusion	Medical contraindication to anticoagulation Stroke or transient ischemic attack within q year Requirement for antiplatelet drug therapy Hyperthyroidism Uncontrolled hypertension Myocardial infraction within 1 month
Arms	
Warfarin	Adjusted dose Warfarin target INR 2.0 – 3.0
Control	placebo

Patient Characteristics

	Warfarin (n = 187)	Placebo (n=191)
Age (years ± SD)	68,0 ± 9,3	67,4 ±9,6
Male (%)	75,9	73,3
Angina (%)	21,9	19,9
Prior myocardial infraction (%)	15,0	12,0
Heart failure (%)	23,5	20,4
Stroke or TIA (%)	3,2	4,2
Intermittent claudication (%)	10,2	4,7
Diabetes (%)	13,9	10,0
Cardiomyopathy (%)	6,4	5,8
History of hypertension (%)	43,3	34,0
Left atrial dimensions (mm ± SD)	45,8±8,1	46,0±8,3
Left ventricular end-diastolic dimensions (mm± SD)	52,4±7,8	57,6±9,0
Arterial vascular bruit (%)	11,8	6,8
Years since diagnosis of AF (%)		
<1	19,8	18,3
1-3	24,6	25,7
4-6	17,1	17,3
>6	38,0	38,2

Unknown	9,5	0,5
Paroxysmal AF (%)	6,4	7,3

*Efficacy analysis up to 28 days after permanent discontinuation of the study medication
**Intention to treat analysis any time during the study

Reference: (14, 18)

7.2.3 EAFT

Randomised open-label placebo-controlled trial (double-blind treatment with aspirin and placebo)
Only summary of trial Group 1 (anticoagulant, aspirin, placebo) (Group 2 – aspirin and placebo)

Lost to follow-up 2
Mean follow-up 2.3 years

Inclusion	Age older than 25 years who had a TIA or minor ischaemic stroke (grade 3 or less on the modified Rankin scale) in the previous 3 months were eligible in atrial fibrillation had been ECG proven at the time or, in paroxysmal atrial fibrillation, in the preceding 24 months, and if ECG showed no evidence of rheumatic valvular diseases
Exclusion	Atrial fibrillation secondary to other disorders such as hyperthyroidism Contraindication to or an absolute indication of aspirin, were taking non-steroid anti-inflammatory drugs,, other anti-platelet-aggregating drugs, or oral anticoagulants, and had no other sources of cardiac emboli such as prosthetic valves, cardiac aneurysm, atrial mycoma, cardiothoracic ratio exceeding 0.65, myocardial infraction in the preceding 3 months, or disorders of blood coagulation. Patients scheduled for carotid endarterectomy or coronary surgery within the next 3 months Chronic and poorly controlled hypertension (diastolic >100 ro systolic > 180 mm HG) Chronic alcoholism Heamorrhagic retinopathy Prior intercranial haemorrhage Expected poor compliance
Arms (group 1)	
Anticoagulant	Free choice of oral anticoagulant (most choosing coumarin derivatives) – target INR 2.5-4.0
Aspirin	Aspirin
Control	Placebo

Patient characteristics

	Anticoagulants (n=225)	Placebo (n=214)
Men (%)	55	58
Mean age (years ±SD)	71 ± 7	70 ± 8
TIA (%)	28	22
Minor ischaemic stroke (%)	72	78
Multiple strokes in year prior (%)	19	25
Minor stroke > 1year (%)	8	7
Hypertension	43	41
Diabetes	12	14
Hypercholesterolaemia	12	7
Regular smoking	19	22
Angina pectoris	11	12
Myocardial infraction	7	10

Reference: (17, 18)

7.2.4 SPAF

Randomised open-label placebo-controlled trial (double-blind treatment with aspirin and placebo)
Primary stroke prevention trial
Randomised to 2 groups: Group I = anticoagulation eligible (warfarin, aspirin, placebo) vs. Group II = ineligible (aspirin, placebo, with age greater than 75 years precluding participation in Group I (this restriction was suspended during the last month of recruitment).
Open label: warfarin vs. aspirin vs. placebo
Double blind: aspirin vs placebo.
Intention-to-treat analysis.
Exclusions: non
Losses to follow up: non
Off therapy: 11 % warfarin, 5% aspirin and 7% placebo
Trial was stopped early after an interim analysis due to the effect of aspirin vs. placebo in Group I (i.e. not because of warfarin effects)

Inclusion	Adults Atrial fibrillation in the preceding 12 months documented by ECG, without prosthetic heart valves, ECG evidence of mitral stenosis and other requirements for or contraindication to aspirin or warfarin Transient, self-limited atrial fibrillation Successful electrical or chemical cardioversion with no recurrence Mitral stenosis (documented by ECG) New York Heart Association functional Class IV congestive heart failure Mitral regurgitation with congestive heart failure and left atrial diameter of more than 5.5 cm Idopathic dilated cardiomyopathy with heart failure Prosthetic heart valve Myocardial infraction within previous 3 months Coronary bypass surgery within previous 1 year Percutaneous trans-luminal coronary angioplasty either previous 3 months Unstable angina pectoris within previous 1 year
Exclusion	Stroke, TIA, or carotid endarterectomy within previous 24 months Life expectancy of less than 24 months because of other medical condition (e.g. metastatic cancer) Chronic renal failure (serumcreatinine contration of more thatn 3.0 mg/dl) Thrombocytopenia with less than 100.000 platelets/mm3 or anaemia with haemoglobin concentration of lessthan 10 g/dl Requirement for warfarin because of prior arterial embolism Severe chronic alcohol habituation Other indication of chronic warfarin therapy, such as pulmonary embolism or deep venous thrombosis within previous 6 months Requirement for treatment with non-steriodal anti-inflammatory drugs Other (13% no reason for exclusion was recorded)
Arms	
Warfarin	Adjusted dose warfarin (target 2.0-4.5)
Aspirin	325 mg/day aspirin
Placebo	Placebo
Characteristic of study population	

	Warfarin	Placebo
N	210	211
Male sex (%)	74	70
Current smoker (%)	13	13
Age		
≤ 60 years	24	20
61-75 years	68	72
≥ 76	8	8
Mean age (years	65	66
Mean blood pressure (mm Hg)		
Systolic	136	135
Diastolic	80	80
Onset of AF (%)		
< 1 year	29	25
≥ 1 year	68	72
On estimate	3	3
Pattern of AF (%)		
Intermittent	38	34
Constant	62	66
Hx hypertension (%)	49	55
Diabetes (%)	12	19
Cervical bruit (%)	4	3
Prior stroke or TIA (%)	8	8
Definite CHF (%)	14	19
Definite angina (%)	9	10
Definite history of myocardial inf. (%)	10	6
Echocaridopraphy		
AD > 5 cm (%)	24	25
Mean LAD (cm)	4.6	4.7
Mitral valve prolapse (%)	5	9
Moderate-to severe Left ventricle dysfunction (%)	14	13

Reference: (15, 18)

7.2.5 BAATA

Randomised open-label controlled trial
Computer-generated randomised. Randomised was blocked according ot three factors: site of recruitment; whether AF was sustained or intermittent; and duration of AF (less than 1 year or more that 1 year)
Intention-to-treat analysis
Exclusions during the trial: 8
Losses to follow up none
Off therapy: 21 in the treatment group
Randomised to two groups (warfarin vs placebo). Open label
Primary stroke prevention trial.
Follow-up average 2.2 years per participant

Inclusion	Adults with chronic sustained or intermittent atrial fibrillation with now evidence of mitral stenosis on two-dimensional ECG (i.e. who had non-reumatic atrial fibrillation), documented by two separate ECGs. Patients with intermittent atrial fibrillation with intermittent atrial fibrillation had to have an ECG documenting AF within 18 months of entry
Exclusion	Transient atrial fibrillation during an acute illness or if cardioversion was planned, ECT evidence of intracardiac thrombus, a left ventricular

	aneurysm, or the presence of severe congestive heart failure or prosthetic heart valves Stroke within previous six months, TIA for which the patient was being treated, any neurologic condition predisposing the patient to intracranial haemorrhage. Clinical indication (e.g. recent thrombophlebitis) or contraindication (e.g. peptic ulcer disease or liver disease) for anticoagulation or if they required aspirin therapy. Normal serum indexes of thyroid function measured at some time after the onset of atrial fibrillation were required.
Arms	
Warfarin	Adjusted dose warfarin target INR 1.5-2.7
Control	No treatment

Characteristics of study group

	Warfarin	Control
N	212	208
Male	158	146
Age at entry (year)	68.5±8.5	67.5±9.3
<60	31	34
60-79	81	88
70-79	82	72
≥ 80	18	14
Intermittent AF	36	34
Duration of AF ≤12 months	68	67
Hypertension	108	106
Cholesterol (mmol)	5.35±1.1	5.33±1.2
Cigarette smoking		
Current	14	20
Former	108	113
Never	90	75
Diabetes	29	34
Angina	48	52
History of Myocardial infraction	22	33
Congestive heart failure	50	59
Non clinical heart disease	105	97
Previous stroke	7	7
Fully independent function status	202	196
Left atrial diameter (mm)	41.9±6.4	40.5±5.8
Mitral regurgitation		
>1+	47	38
≤1+	140	145
Mitral annular calcification	70	59

Reference: (13, 18)

7.2.6 SPINAF

Randomised double blinded placebo controlled trial
Randomly assigne daccordin to list generated by the Co-ordianatin Center
Primary and secondary storke prevention tiral
Losses to follow up: 12 in control group an d7 in warfarin group
Exclusions: 4 in control group and 9 in warfarin group (in primary prevention group=
The trial was stopped at an interim analysis after a man follow up of 1.7 years per participant

	USA
Participants	Total number 571 100% male
Inclusion	Male veterans of any age, without ECG evidence rheumatic heart disease, who had atrial fibrillation documented by two ECGs at least four weeks apart. Base line prothombin-time ratio had to be within normal range Patients who had previously received oral anticoagulation therapy for more than one month were required to discontinue warfarin treatment for at least six months before randomization Patients with intermittent atrial fibrillation. Definite indication for anticoagualation or antiplatelet agents, Prosthetic heart valve, Mitral stenosis, Active thromboembolic disease, Coronary-artery by-pass surgery, Intracardiac thrombus, Myocardial infraction within 1 month.
Exclusion	Contraindicationn to anticoagulation, chronic alcoholism or psychological, social or genera condition rendering the patient unsuitable for anticoagulation. Coexisting medical disorder, Hemostasis disorder, Documented peptic ulcer disease within 2 years, known esophageal varices, or history of intra cranial haemorrhage, History of gastrointestinal haemorrhage within 2 years. Planned surgery or invasive procedure, Laboratory abnormalities; haematocrit<32%, platelet count >1000.000/mm3,serum aspartate aminotransferase, serum alanine aminotransferase, ro alkaline phosphatase 2 times upper limit of normal; guaic-positive stool; or >5 red cells per high-power field in urine. Uncontrolled hypertension (>180/105 mmHg) Bacterial endocarditis, Atrial tumor. Received anticoagulation within past 6 months for more than 1 continuous months, use fo aspirin or non-steroidal anti-inflammatory agent, ECG interpretable, TIA within 5 years, Previous cerebral infraction, Hyperthyroidism, Cardioversion planned Unstable angina
Arms	
Warfarin	Dose adjusted warfarin (target prothrombin-time ratio 1.2 – 1.5 ~ INR 1.4-2.8)
Placebo	Placebo

Characteristics of study population

	Placebo (n=265)	Warfarin (n = 260)
Age (years)	67±7	67±7
Duration of documented atrial fibrillation (years)	8.2±9.5	7.6±8.9
Ejection fraction (%)	48±14	48±12
Left atrial size (cm)	2.30±0.40	2.32±0.39
Duration of documented atrial fibrillatin <6 months -n (%)	36(14)	29 (11)
History of hypertension -n (%)	163 (62)	142 (55)
Cigarette smoking –n (%)		
Current	45 (17)	41 (16)
Former (within 5 years)	23 (11)	29 (13)
History of diabetes- n (%)	52 (20)	45 (17)
Active angina –n (%)	60 (23)	57 (22)
Myocardial infarction – n (%)	55 (21)	45 (17)
Anterior-wall Q-wave	13 (5)	15 (6)

Inferior-wall Q-wave	23 (9)	24 (9)
History of congestive heart failure – n (%)	80 (30)	80 (31)
Carotid stenosis	19 (12)	17 (10)
Mitral regurgitation ≥ 2+	38 (19)	40 (19)
Mitral annular calcification	48 (18)	37 (14)
Silent cerebral infraction on CT scanning	33 (12)	27 (10)
No Clinical heart disease	7 (3)	9 (3)

Reference: (16, 18)

7.2.7 RE-LY

Randomised clinical trial
Dabigatran 110 mg vs. dabigatran 150 mg blinded
Dabigatran vs. warfarin open-label
18.133 patients
Discontinuation rate, dabigatran 110 mg 14.5%, dabigatran 150 mg 15,5% and warfarin 10.2%
Lost to follow-up 20 patients
Medial duration of follow-up 2.0 years

Participants	18.133 patients recruited from 951 clinical centers in 44 countries
Inclusion	Atrial fibrillation documented on electrocardiography performed at screening or within 6 months before hand and at least one of the following characteristics. Previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension or coronary artery disease
Exclusion	Presence of severe heart –valve disorder, stroke within 14 days or severe stroke within 6 months before screening, a condition that increased the risk of hemorrhage, a creatinine clearance of less than 30 ml per minute, active liver disease, and pregnancy

Arms
Warfarin — Dose adjusted warfarin (INR 2.0-2.0 – with INR measured at least monthly)
Dabigatran 110, mg
Dabigatran 150 mg

Characteristics of study population

	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Age (years)	71.4 ± 8.6	71.5 ± 8.8	71.6 ± 8.6
Weight (kg)	82.9 ± 19.9	82.5 ± 19.4	82.7 ± 19.7
Blod pressure (mm Hg)			
Systolic	130.8 ± 17.5	131.0 ± 17.6	131.2 ± 17.4
Diastolic	77.0 ± 10.6	77.0 ± 10.6	77.1 ± 10.4
Male (%)	64.3	63.2	63.3
Type of atrial fibrillation (%)			
Persistent	32.4	31.4	32.0
Paroxysmal	32.1	32.6	33.8
Permanent	35.4	36.0	34.1
CHADS2 score (%)			
0 or 1	32.6	32.2	30.9
2	34.7	35.2	37.0
3-6	32.7	32.6	32.1
Previous stroke or TIA (%)	19.9	20.3	19.8
Prior myocardial infraction (%)	16.8	16.9	16.1

Heart failure (%)	32.2	31.8	31.9
Diabetes mellitus (%)	23.4	23.1	23.4
Hypertension (%)	78.8	78.9	78.9
Medications in use at baseline (%)			
Aspirin	40.0	38.7	40.6
ARB or ACE inhibitor	66.3	66.7	65.5
Beta-blocker	62.9	63.7	61.8
Amiodarone	10.4	10.9	10.7
Statin	44.9	43.9	44.9
Proton-pump inhibitor	13.5	13.9	13.8
H2-receptor antagonist	3.7	4.0	4.3
Long-term VKA thearpy	50.1	50.2	48.6

Reference: (29, 30)

7.2.8 ROCKET-AF

Double-blind randomised trial (mulit-center , randomised, double-blind, double-dummy event- driven trial)
Per-protocol, as treated primary analysis
Discontinuation rate: rivaroxaban 23.7%, warfarin 22.2%
Losses to followup 32
Because of violation in GCP guidelines on sit that made the data unreliable, 93 patients (50 in rivaroxaban group and 43 in warfarin group) were exclude form all efficacy analysis before unbinding.
Median follow-up was 707 days, media duration of treatment exposure was 590 days

Participants	14.264 patients at 1178 paticipatin sites in 45 countries Women 39.7%
Inclusion	Patients with non-valvular atrial fibrillation, documented on ECG, who were at moderate-to-high risk for stroke. Elevated risk was indicated by a history of stroke, transient ischemic attack, or systemic embolism or at least two of the following risk factors: heart failure or a left ventricular ejection fraction of 35% or less hypertension, an age of 75 years or more, or the present of diabetes (i.e. a CHADS2 score of 2 or more, on a scale ranging from 1 to 6)
Exclusion	
Arms	
Warfarin	Dose adjusted warfarin (INR 2.0-2.0 – with INR measured at least monthly)
Rivaroxaban	Rivaroxaban 20 mg daily

Patient Characteristics (intention to treat population at baseline)

	Rivaroxaban	Warfarin
Age (y)		
Median	73	73
Interquartile range	65-78	65-78
Female (%)	39.7	39.7
Body-mass index (kg/m2)		
Median	28.3	28.1
Interquartile range	25.2 – 32.1	25.1 – 31.8
Blood pressure (mmHg)		
Systolic		
Median	130	130
Interquartile range	120 - 140	120 – 140
Diastolic		
Median	80	80
Interquartile range	70 - 85	70 – 85
Type of atrial fibrillation (%)		

Persistent	81.1	80.8
Paroxysmal	17.5	17.8
Newly diagnosed or new onset	1.4	1.4
Previous medication use (%)		
Aspirin	36.3	36.7
Vitamin K antagonist	62.3	62.5
CHADS2 score		
Mean score (± SD)	3.48 ± 0.94	3.46 ± 0.95
Score (%)		
2		
3	13.0	13.1
4	24.9	44.3
5	13.1	12.4
6	1.7	2.2
Co-existing condition (%)		
Previous stroke, systemic embolism or TIA	54.9	54.6
Congestive heart failure	62.6	62.3
Hypertension	90.3	90.8
Diabetes mellitus	40.4	39.5
Previous myocardial infraction	16.6	18.0
Peripheral vascular disease	5.6	6.1
Chronic obstructive pulmonary disease	10.6	10.4
Creatinine clearance		
Median	67	67
Interquartile range	52 - 88	52 – 86

Reference: (28)

7.2.9 ARISTOTLE

Randomised double blinded trial (, randomised, double-blind, double-dummy design)
Randomisation was stratified according to whether patients had received warfarin previously and according to clinical site. Apixaban or matching placebo was administered twice daily, and warfarin or matching placebo.
Withdrawal of consent in 93 patiens in apixaban group (1.0%) and 107 patients in warfarin group (1.2%)
Loss to follow-up 35 patients in apixaban group (0.4%) and 34 in warfarin group (0.44%)

Median duration of follow-up 1.8 years

Participants	18.201 patients at 1034 clinical sites in 39 countries
Inclusion	Atrial fibrillation of flutter at enrolment or two or more episodes of atrial fibrillation or flutter, as documented by ECG, at least 2 weeks part in the 12 months before enrolment. In addition at least one of following risk factors for stroke was required: age of at least 75 years, previous stroke, TIA, or systemic embolism, symptomatic heart failure within the previous 3 months or left ventricular ejection fraction oof no more than 40%, diabetes mellitus, or hypertension requiring pharmacologic treatment.
Exclusion	Atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, conditions other that atrial fibrillation that required anticoagulation (e.g. a prosthetic heart valve), stroke with in the previous 7 days, a need for aspirin at a dose of > 165 mg a day or for both aspirin and clopidogrel, and severe renal insufficiency (serum creatinine level of > 2.5 mg per decilitre.
Arms	
Warfarin	Dose adjusted warfarin (INR 2.0 – 3.0)
Apixaban	5 mg twice daily (2.5 mg dose were used in subset age > 18 years, body

weight < 60 kg or serum creatinine level of 1.5 mg per decilitre or more)

Characteristics of study population

	Apixaban	Warfarin
Age (y)		
Median	70	70
Interquartile range	63 - 76	63 – 76
Female (%)	35.5	35.0
Region (5)		
North America	24.7	24.5
Latin America	19.1	19.0
Europe	40.3	40.4
Asian Pacific	16.0	16.1
Systolic blood pressure (mmHg)		
Medial	130	130
Interquartile range	120 - 140	120 – 140
Weight (kg)		
Median	82	82
Interquartile range	70 - 96	70 – 95
Prior myocardial infraction (%)	14.5	13.9
Prior clinically relevant or spontaneous bleeding (%)	16.7	16.7
History of fall within previous year (%)	4.2	4.0
Type of atrial fibrillation (%)		
Paroxysmal	15.1	15.5
Persistent or permanent	84.9	84.4
Prior use of vitamin K antagonist for > 30 consecutive days (%)	57.1	57.2
Qualifying risk factors		
Age ≥ 75 years (%)	31.2	31.1
Prior stroke, TIA, or systemic embolism (%)	19.2	19.7
Heart failure or reduced left ventricular ejection fraction (%)	35.5	35.4
Diabetes (%)	25.0	24.9
Hypertension requiring treatment (%)	87.3	87.3
CHADS2 score (%)		
1	34.0	34.0
2	35.8	35.8
≥3	30.2	30.2

Reference (31)

7.3 Appendix 3: Iterative process to define value tree/effect table

7.3.1 First iteration

The initial value tree was constructed based on discussions/brain-storm in a face-to-face meeting on 30st of June 2012, where the benefits of the use of warfarin in patients with non-valvular atrial fibrillation were discussed, along with the general harms potentially associated with warfarin therapy (see figure 29). This initial value tree was built only on the medical relevance of both the Benefit and Risk criteria (some of which were also primary criteria of clinical trials), but regardless of potential overlap in the criteria definitions or of availability of suitable data for subsequent modelling.

Further it was planned to extract data from existing reviews/meta-analysis of warfarin versus placebo/no treatment for primary prevention of stroke in atrial fibrillation

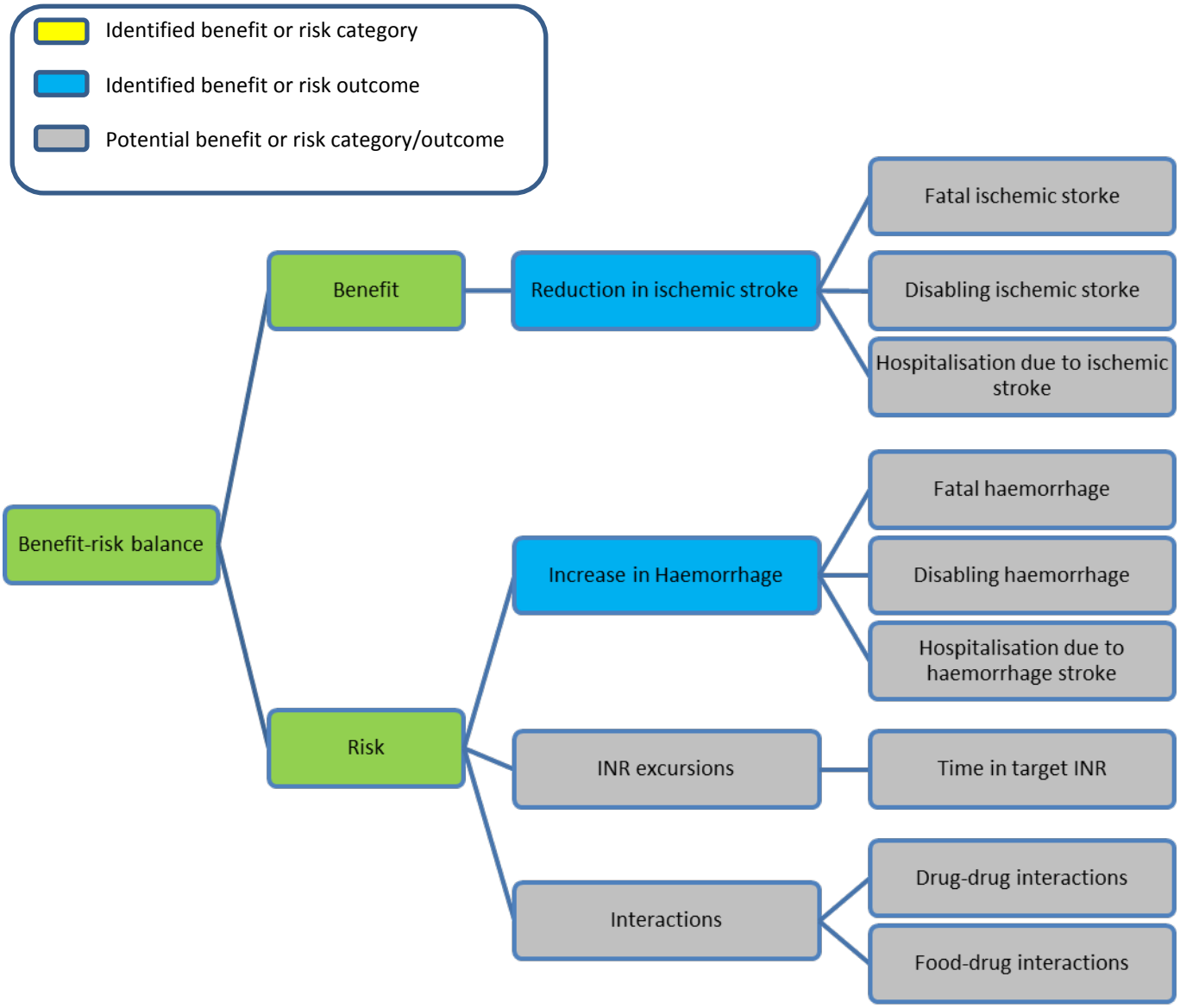


Figure 29: Initial value tree for the benefit-risk assessment of warfarin versus placebo.

A systematic literature review was conducted to identify relevant meta-analysis studies. The literature search found several reviews and meta-analyses for the prevention of stroke in atrial fibrillation, all based on the same 5-6 randomised clinical trials (AFASAK I (12), BAATAF (13), CAFA (14), SPIN I (15) and SPINAF (16) and EAFT (17). The Cochran review by Aguilar and Hart (18) included criteria which could best fit our initial outcomes in the value tree, and therefore this review was chosen to be the base for our benefit risk assessment of warfarin versus no treatment in atrial fibrillation.

Table 20: Data source table, identified endpoints and definitions

	Category	Endpoint	Definition	Study Type
Benefit	Reduction in Ischaemic stroke	All-cause mortality	Death from any cause (vascular and nonvascular) within 30 days from onset of stroke symptoms. For this outcome, results of published data, which included % of patients with prior stroke or TIA, were used.	Meta-analysis of RCTs (18)
		Ischemic strokes (including both fatal and non-fatal).	Diagnosis based on clinical features not requiring confirmation by neuroimaging. Asymptomatic brain infarcts detected on neuroimaging were not included. Hemorrhagic transformation of ischemic strokes were considered with ischemic strokes.	Meta-analysis of RCTs (18)
Risk	Increase in haemorrhage	All intracranial haemorrhage.	This included intraparenchymal, subdural and epidural hematomas, and subarachnoid haemorrhage based on clinical diagnosis by the investigators and usually confirmed by computerized tomography (CT) scan or post mortem. It should be noted that intracranial haemorrhagic strokes are generally associated with worse outcomes than ischaemic strokes.	Meta-analysis of RCTs (18)
		Major extracranial haemorrhage.	Major extracranial haemorrhage. Criteria varied between the studies considered in this analysis. From the AFI database, those which required transfusion of two or more units of red blood cells, hospitalization, or invasive procedures to control bleeding and those that resulted in death or permanent functional impairment (e.g. blindness) were included.	Meta-analysis of RCTs (18)

The criteria 'all-cause mortality' was included since it was felt that fatal events should be considered on their own, and not grouped with possible minor ischaemic stroke. However, at this stage 'all-cause mortality' may include both fatal ischaemic stroke and fatal haemorrhage events. In this first iteration the customised value tree was as shown in figure 30. In addition, it was decided that the risk criteria "INR excursions" should not be included, since problems in connection to INR excursions would already be represented in the data from the "medical" endpoint (i.e. haemorrhagic events or failure to prevent the ischemic stroke risk). The inconvenience criteria were also removed in the customised value tree, to limit the benefit risk problem to a merely medical problem. Please note that the Inconvenience criteria does not exist in the initial Value Tree shown above. Here we should rather discuss the "pruning" of the Interactions criteria (what was the reason? did we have data to quantify this?)

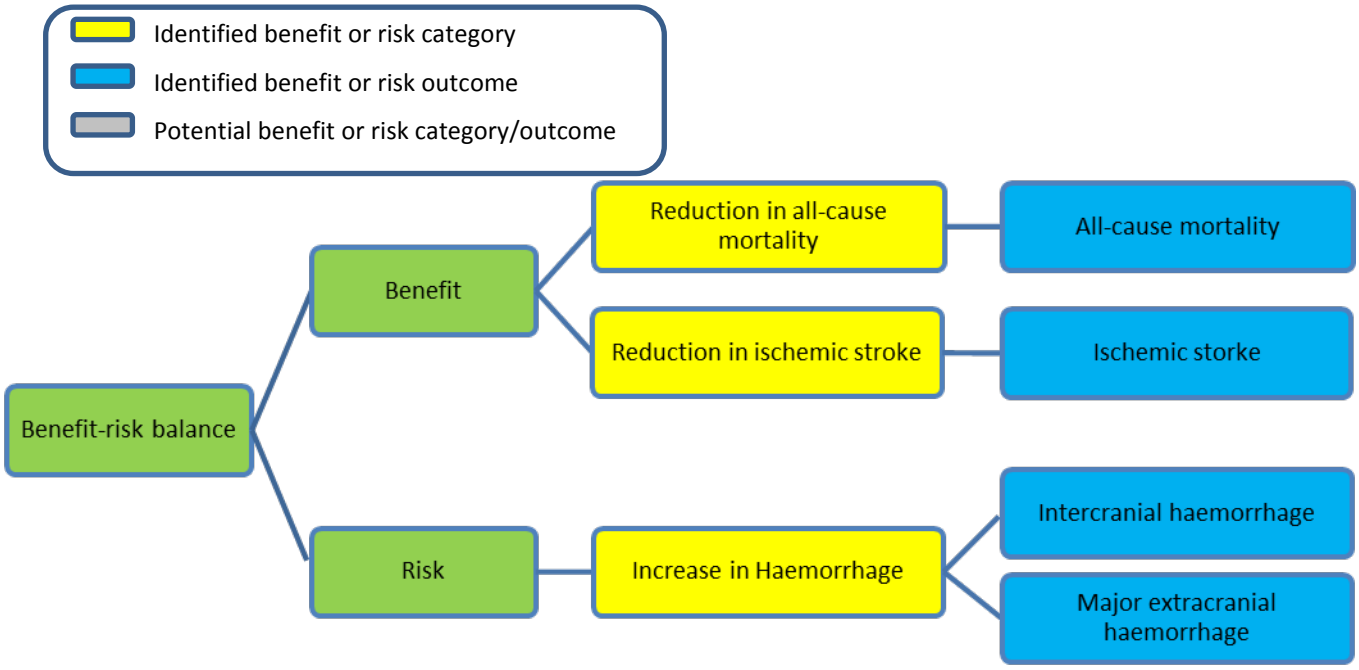


Figure 30: Customised value tree for the benefit risk assessment of no treatment and warfarin

7.3.2 Second iteration

The value tree/criteria identified in the first iteration has problems in connection to double counting, some fatal events are included into two criteria, such as fatal ischaemic strokes events which is included in the criteria "all-cause mortality" and in "ischaemic stroke". It was also found that the criteria "Ischaemic stroke" include too large a range of events, which makes it difficult to weight the importance of this criteria relative to the others.

It was felt that, if the criteria "Inconvenience of drug administration" should be taken into account (when and if measurable), it should only be after the B-R of drug/comparators has been made based on its medical/pharmacological properties only. This is because a borderline negative B-R might be unduly shifted to positive if just only based on this convenience criteria.

The second iteration of the value tree was based from the learning's from the first version. I was decided to not limit the data evidence from published reviews or meta-analysis, but also use published data from the individual studies. From the literature search 5 studies comparing treatment with warfarin and placebo/no treatment for primary prevention of stroke in atrial fibrillation (12-16) was identified. See Appendix 2: Summary of randomised clinical trials for summaries of the included RCTs. The table below shows the possible relevant endpoints identified in the 5 RCTs, and a grouping of endpoints to be used, explains the proposed modifications of the value tree criteria.

Table 21: The table include the available endpoints from the 5 RCTs identified; the colours represent possible outcome grouping into disabling ischaemic stroke, non-disabling ischaemic stroke, Major Haemorrhage and Minor Haemorrhage.

Study	----------Ischaemic stroke endpoints----------				----------Haemorrhage endpoints----------		
AFASAK	**Fatal ischaemic stroke**	**Disabling ischaemic stroke** Definite functional disability a month after event	**Non-disabling ischaemic stroke** Not leaving definite functional disability a month after onset	**Minor ischaemic stroke** Other	**Fatal bleed**	**Major bleed** Requiring medical intervention	**Minor bleed**
BAATAF	**Fatal ischaemic stroke**	**Severe ischaemic stroke** Deficits that preclude independent functioning	**Moderate ischaemic stroke** Substantial deficit but with independent function	**Mild ischaemic stroke** Little of no persistent deficient		**Major bleed** Intracranial, fatal or bleeding leading to transfusion of four or more unit of blood within 48 hours*^	**Minor bleed** Other bleeding events
CAFA		***Non-lacunar stroke***	***Lacunar stroke***		**Fatal bleed**	**Life threatening or major bleed**	
SPAF	**Fatal ischaemic stroke**	**Moderately to severely disabling**		**Minimally**	**Fatal**	**Major Bleed** CNS, hospitalization with transfusion and or/surgery or permanent residual impairment^	
SPINAF	**Fatal Cerebral infraction**	**Cerebral infraction with major impairment** Independence lost at 30 day after the event	**Cerebral infraction with minor impairment** Independence at 30 days after the event, despite impairment	**Cerebral infraction with no impairment** No impairment at 30 days after the event	**Fatal**	**Major Bleed** Required blood transfusion, emergency procedure or admission to an intensive care unit ^	**Minor Bleed** Other bleeding events

*Fatal events can be subtracted, ^ CNC haemorrhage can be excluded

The data from the RCTs and the learning's from the previous iteration of the value tree opened the discussion to 3 possible value trees to be evaluated for further use in analysis in the benefit-risk assessment of warfarin versus control for the prevention of atrial fibrillation.

Value tree nr 1 with corresponding data source table (please note the absence of any convenience criteria in the data sources used for this option)

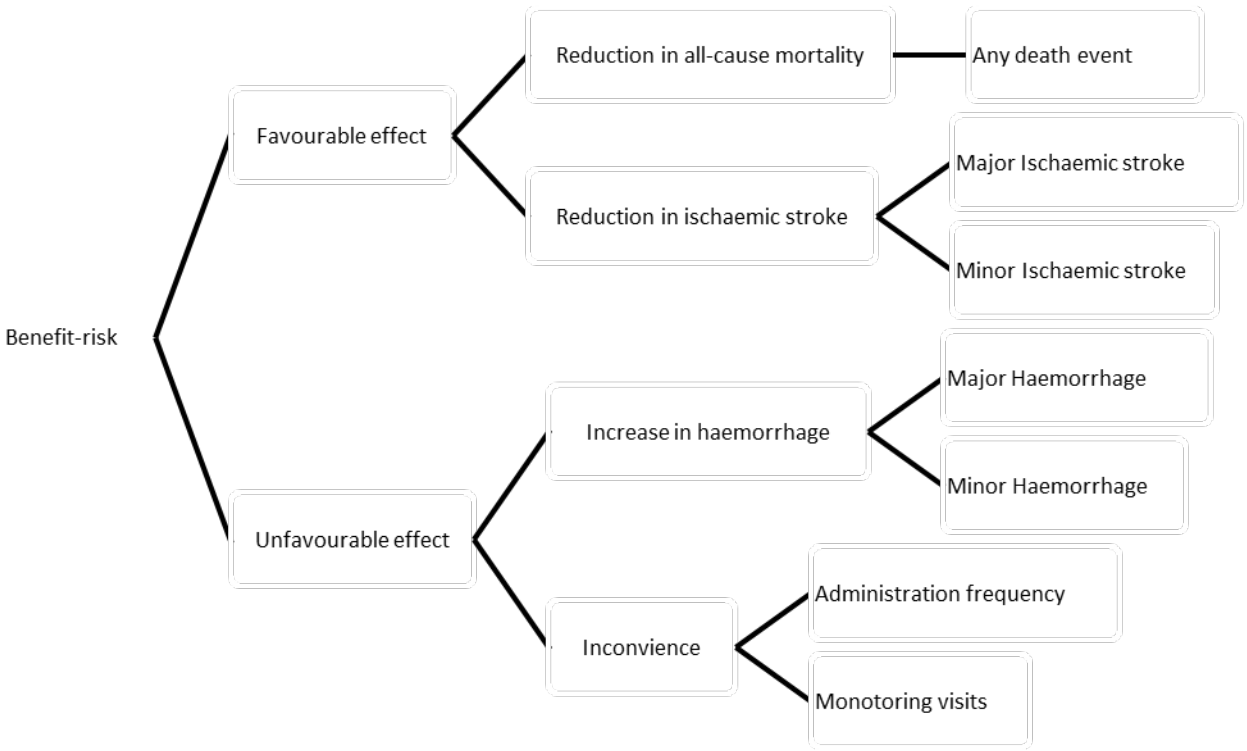


Figure 31: Value tree number 1 of second iteration

Table 22: Data source table corresponding to value tree number 1

	Category	Outcome	Major Haemorrhage	Study
Benefits	Reduction in all-cause mortality	All-cause mortality*		Meta-analysis (18)
	Reduction in ischaemic stroke	Major stroke	Disability with or without independent function a month after event (non-fatal)	AFASAK (12)
				BAATAF (13)
				SPINAF (16)
				SPAF (15)
		Minor stroke	Non-disabling a month after event (non-fatal)	AFASAK (12)
				BAATAF (13)
				SPINAF (16)
				SPAF (15)
Risk	Increase in haemorrhage	Major haemorrhage	Requiring medical intervention or CNS haemorrhage (non-fatal)	AFASAK (12)
				BAATAF (13)
				CAFA (14)
				SPINAF (16)
				SPAF (15)
		Minor haemorrhage	Other bleeding events (non-fatal)	AFASAK (12)
				BAATAF (13)
				CAFA (14)
				SPINAF (16)

Value tree nr 2 with corresponding data source table (same comment as above for convenience criteria)

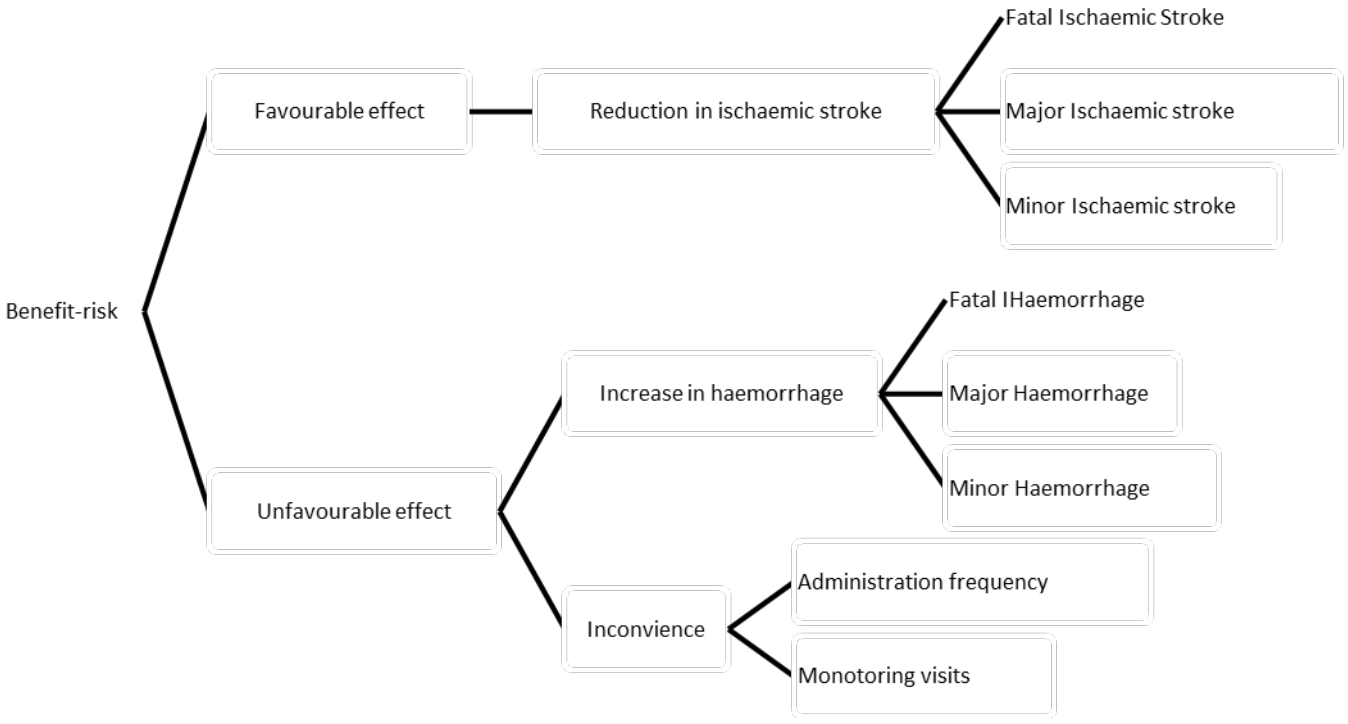


Figure 32: Value tree number 2 of second iteration

Table 23: Data source table corresponding to value tree number 2

	Category	Outcome		Study
Benefits	Reduction in ischaemic stroke	Fatal ischaemic stroke		AFASAK (12)
				BAATAF (13)
				SPINAF (16)
				SPAF (15)
		Major ischaemic stroke	Disability with or without independent function a month after event (non-fatal)	AFASAK (12)
				BAATAF (13)
				SPINAF (16)
				SPAF (15)
		Minor ischaemic stroke	Non-disabling a month after event (non-fatal)	AFASAK (12)
				BAATAF (13)
				SPINAF (16)
				SPAF (15)
Risk	Increase in haemorrhage	Fatal haemorrhage		AFASAK (12)
				BAATAF (13)
				CAFA (14)
				SPINAF (16)
				SPAF (15)
		Major haemorrhage	Requiring medical intervention or CNS haemorrhage (non-fatal)	AFASAK (12)
				BAATAF (13)
				CAFA (14)
				SPINAF (16)
				SPAF (15)
		Minor haemorrhage	Other bleeding events (non-fatal)	AFASAK (12)
				BAATAF (13)
				SPINAF (16)

Value tree number 1 and 2 are quite different except for the way fatal events is included, in value tree number 1 all fatal events are included in the criteria 'all-cause mortality' while value tree number 2 includes only fatal events from ischaemic stroke and haemorrhages in the two criteria 'fatal ischaemic stroke' and 'fatal haemorrhage'.

Value tree nr 3 with corresponding data source table (same comment as above regarding convenience criteria)

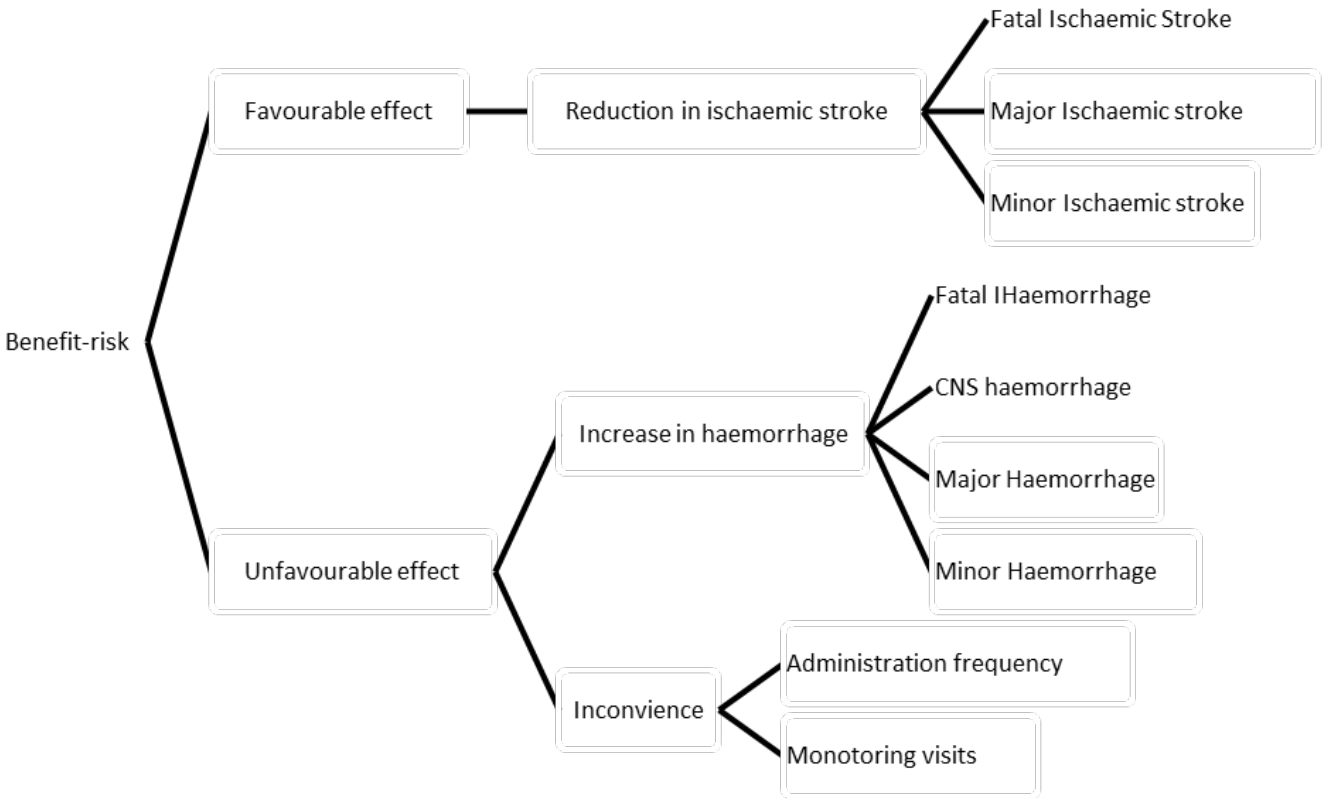


Figure 33: Value tree number 3 (second iteration)

Table 24: Data source table corresponding to value tree number 3

	Category	Outcome		Study
Benefits	Reduction in ischaemic stroke	Fatal ischaemic stroke		AFASAK
				BAATAF
				SPINAF
				SPAF
		Major ischaemic stroke	Disability with or without independent function a month after event (non-fatal)	AFASAK
				BAATAF
				SPINAF
				SPAF
		Minor ischaemic stroke	Non-disabling a month after event (non-fatal)	AFASAK
				BAATAF
				SPINAF
				SPAF
Risk	Increase in haemorrhage	Fatal haemorrhage		AFASAK
				BAATAF
				CAFA
				SPINAF
				SPAF
		CNS haemorrhage (non-fatal)	All non-fatal CNS haemorrhage	BAATAF
				SPINAF
				SPAF
		Major haemorrhage	Requiring medical intervention (non-fatal, and non-CNS)	BAATAF
				SPINAF
				SPAF
		Minor haemorrhage		AFASAK
				BAATAF
				SPINAF

A differential weighting of death from ischaemic stroke, and from haemorrhagic events was discussed. It seemed finally medically logical that they both carry the same weight since we are interested in avoiding death whatever the cause. Therefore it was decided to move forward with value tree number 1, which include the criteria 'all-cause mortality'. Further on, it was decided to include value tree number 3 to illustrate the large variety in the grouped "major haemorrhage" which could include both disabling and non-disabling events. But the tree was not used for analysis because the gap between data availability and precision of the criteria defined in the tree was considered too large.

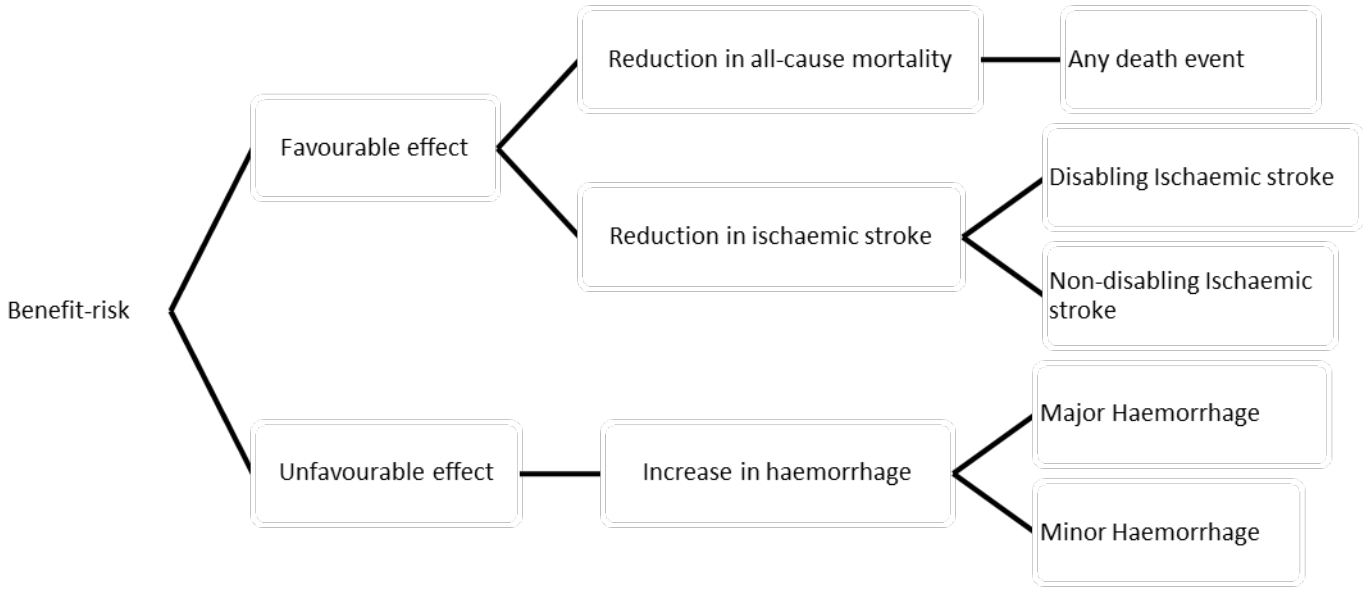
In the final step the value tree was modified slightly, by excluding the inconvenience criteria, again to limit the benefit risk problem to a purely medical problem. It was felt that taking the inconvenience criteria into account (when and if measurable) should only take place AFTER the B-R of drug/comparators has been made based only on its pharmacological properties, because a border-line negative B-R balance might be improperly shifted to positive if based only on a convenience criteria.

This successive iteration in the build-up of a final Value Tree shows in this warfarin example how difficult it may be to translate a complex medical problem having multiple and heterogenic aspects into a consistent, medically relevant

and statistically performing model. In the example shown above, a multiplicity of issues had to be addressed by the team in order to come up with a satisfying model: availability of data, reliability and consistency of the same data across a large data set, medical relevance of chosen criteria even though they might have been clinical endpoints of Clinical Trials, ability of quantify of some important clinical criteria, duplication of patient counting through overlapping of criteria, etc.

The build-up of a Value Tree is a critical step in the process of a Benefit-Risk assessment as its final design (i.e. the model tested) may have a major influence in the final result of a B-R balance assessment.

7.4 Appendix 4: SMAA analysis using JSMAA software



7.4.1 Data

In this analysis, a Bayesian approach is adopted to derive the distributions for the two alternatives on all criteria. For all criteria, the distribution of event rates per patient-year is updated using observed rates in 5 RCTs from non-informative prior Beta(a,b) = Beta(1,1).

Table 25: a and b parameters for the beta distribution of event rates for all criteria

	Warfarin		Control	
	a	b	a	b
All-cause Mortality	70	1773.2	100	1757.3
Disabling Ischaemic Stroke	12	1552.4	32	1534.5
Major Haemorrhage	22	1785.4	17	1797.8
Non-disabling Ischaemic Stroke	5	1559.4	29	1534.5
Minor Haemorrhage	117	1195.4	61	1797.8

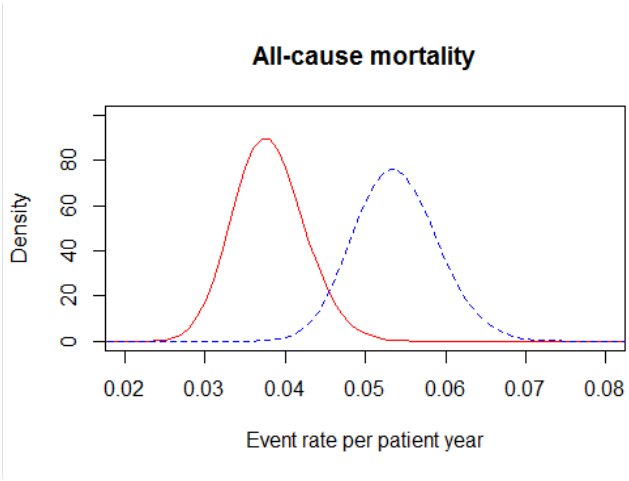
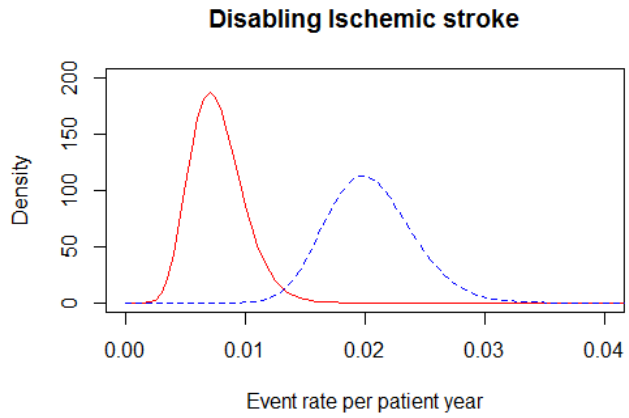
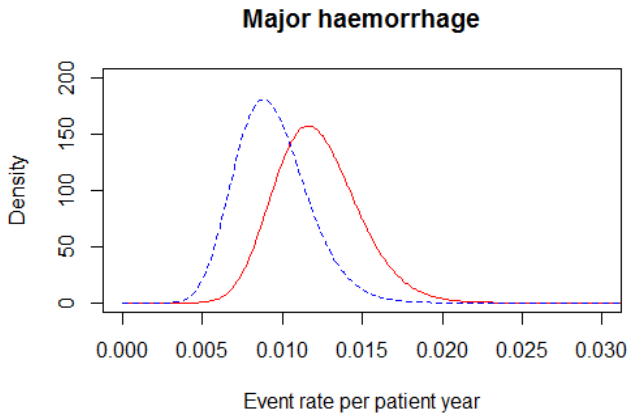
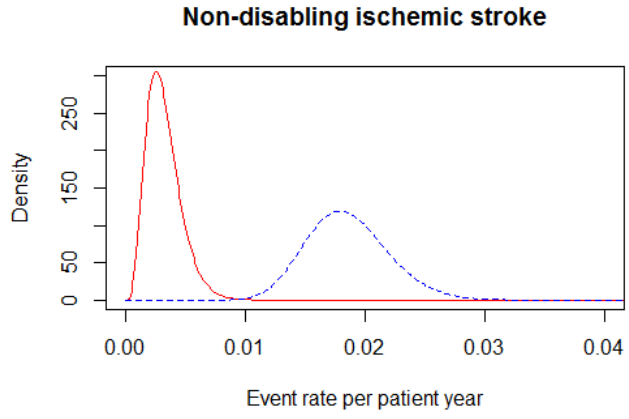
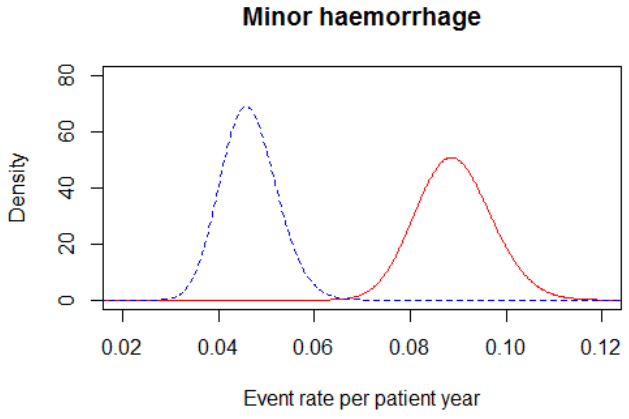


Figure 34: Distribution of warfarin (red solid line) and control (blue broken line) for all criteria









7.4.2 Value function

The value function of each criterion is a function taking a value in range [0,1] with 0 for the least preferred value and 1 for the most preferred value.

In this analysis we use linear value function (a limitation of the JSMAA software). The least preferred value and most preferred value of each criterion are the maximum upper end and the minimum lower end of the data for the two alternatives. The shape of value function for each criterion is presented below

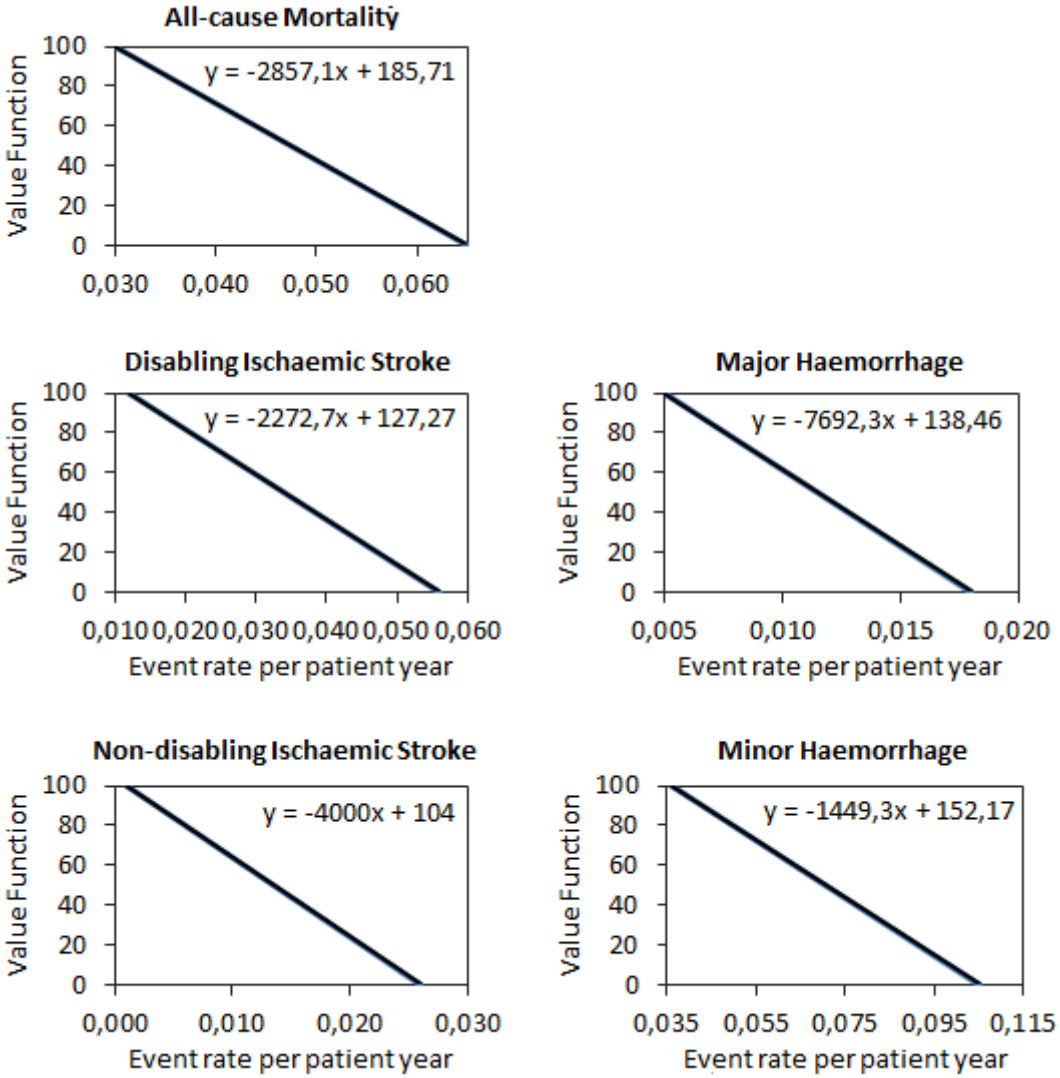


Figure 35: Value function for all benefit-risk criteria (criteria)

7.4.3 Weights

The weights was assigned so that the relative contribution (weight × value) of an additional event to benefit risk score corresponds to the relative disutility described in section 2.7 Quantify and interpret key benefit-risk metrics. Table 26 and table 27 shows the scale of the value function used in the SMAA analysis and the weights assigned to each criterion, for scenario A and B respectively. The three columns to the right describe the effect of one additional event on each criterion to the benefit risk score. The column 'value' describes the value of an additional event given the value function. The 'contribution to the overall BR' column gives the contribution of an additional event for the given criteria to the overall benefit risk score (weight × value). The column 'normalised' corresponds to the normalised weight of scenario A and B respectively (see section 2.7.1 Exploring the benefit-risk balance using SMAA - Normalising weights.

Table 26: Scenario A. scale of value function and weights for each benefit-risk criteria.

Criteria	Value function scale		Weight	Effect of one additional event		
	min	max		Value	Contribution to overall BR	Normalised*
All-cause Mortality	0.03	0.065	0.4160	-2.86	-1.19	0.412
Disabling Ischaemic Stroke	0.012	0.056	0.3050	-2.27	-0.69	0.240
Major Haemorrhage	0.005	0.018	0.0535	-7.69	-0.41	0.143
Non-disabling Ischaemic Stroke	0.001	0.026	0.1030	-4.00	-0.41	0.143
Minor Haemorrhage	0.036	0.105	0.1225	-1.45	-0.18	0.062

* Normalised contribution are calculated as the proportion of its contribution to the total contribution

Table 27: Scenario B. scale of value function and weights for each benefit-risk criteria.

Criteria	Value function scale		Weight	Effect of one additional event		
				Value	Contribution	Normalised*
All-cause Mortality	0.03	0.065	0.4022	-2.86	-1.15	0.376
Disabling Ischaemic Stroke	0.012	0.056	0.2937	-2.27	-0.67	0.219
Major Haemorrhage	0.005	0.018	0.0871	-7.69	-0.67	0.219
Non-disabling Ischaemic Stroke	0.001	0.026	0.0990	-4.00	-0.40	0.130
Minor Haemorrhage	0.036	0.105	0.1180	-1.45	-0.17	0.056

* Normalised contribution are calculated as the proportion of its contribution to the total contribution

7.4.4 Results

Scenario A

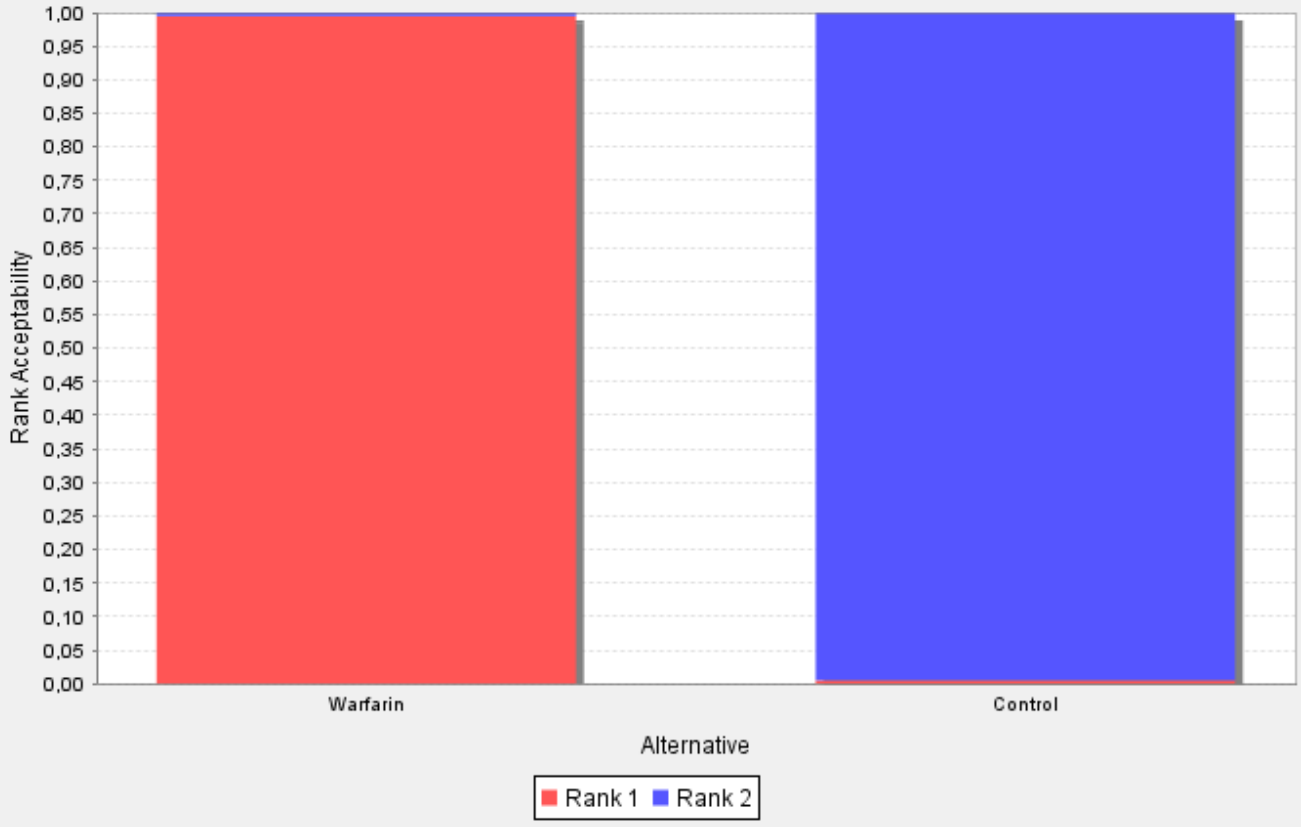
Preferences

CARDINAL | Preference information

Criterion	Scale	Weight constraint	
All-cause Mortality	[0,03 - 0,06]	Exact	0.416
Major Ischemic Stroke	[0,01 - 0,06]	Exact	0.305
Major Haemorrhage	[0,01 - 0,02]	Exact	0.0535
Minor Ischemic Stroke	[0,00 - 0,03]	Exact	0.103
Minor Haemorrhage	[0,04 - 0,11]	Exact	0.1225

Rank acceptability indices

Alternative	Rank 1	Rank 2
Warfarin	0,99	0,01
Control	0,01	0,99



Scenario B

Preferences

CARDINAL | Preference information

Criterion	Scale	Weight constraint	
All-cause Mortality	[0,03 - 0,06]	Exact	0.4022
Major Ischemic Stroke	[0,01 - 0,06]	Exact	0.2937
Major Haemorrhage	[0,01 - 0,02]	Exact	0.0871
Minor Ischemic Stroke	[0,00 - 0,03]	Exact	0.099
Minor Haemorrhage	[0,04 - 0,11]	Exact	0.118

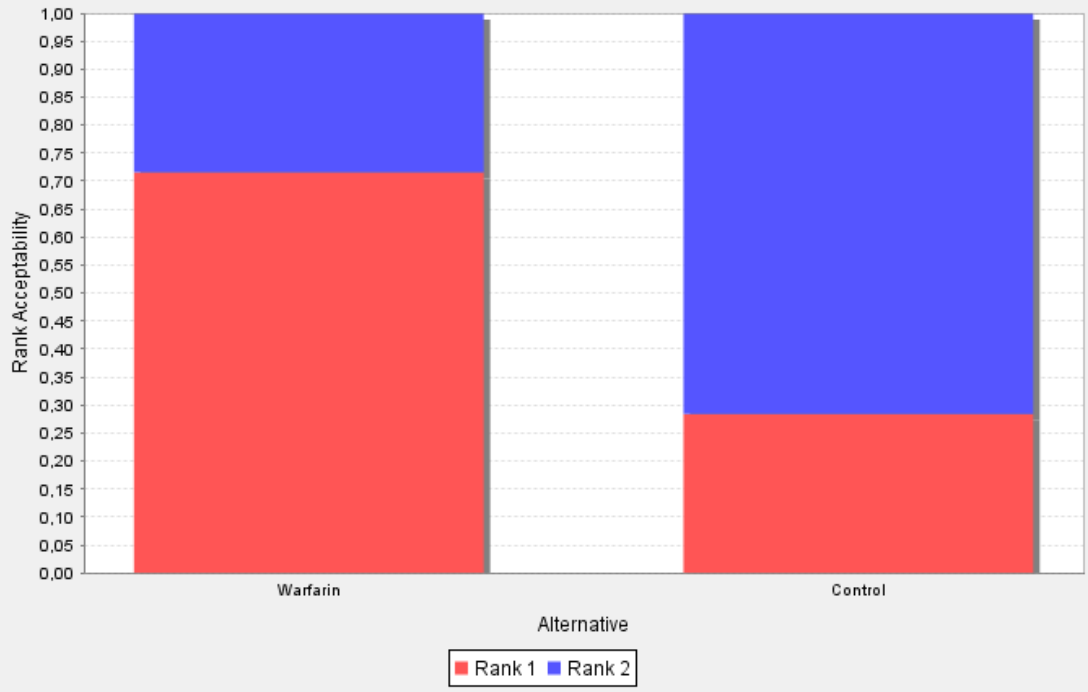
Rank acceptability indices

Alternative	Rank 1	Rank 2
Warfarin	0,99	0,01
Control	0,01	0,99

Missing weights

Rank acceptability indices

Alternative	Rank 1	Rank 2
Warfarin	0,72	0,28
Control	0,28	0,72



Central weight vectors

Alternative	CF	All-cause Mor...	Major Ischemi...	Major Haemor...	Minor Ischemi...	Minor Haemo...
Warfarin	0,99	0,23	0,22	0,18	0,24	0,14
Control	0,81	0,13	0,14	0,26	0,11	0,35