Benefit-risk assessment in a post-market setting: A case study integrating real-life experience into benefit-risk methodology

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Abstract:	<p>Purpose Difficulties may be encountered when undertaking a benefit-risk assessment for an older product with well-established use but with a benefit-risk balance that may have changed over time. This case study investigates this specific situation by applying a formal benefit-risk framework to assess the benefit-risk balance of warfarin for primary prevention of patients with atrial fibrillation.</p> <p>Methods We used the qualitative framework BRAT as the starting point of the benefit-risk analysis, bringing together the relevant available evidence. We explored the use of a quantitative method (Stochastic Multi-criteria Acceptability Analysis - SMAA) to demonstrate how uncertainties and preferences on multiple criteria can be integrated into a single measure to reduce cognitive burden and increase transparency in decision-making.</p> <p>Results Our benefit-risk model found that warfarin is favourable compared to placebo for the primary prevention of stroke in patients with atrial fibrillation. This favourable benefit-risk balance is fairly robust to differences in preferences. The probability of a favourable benefit-risk for warfarin against placebo is high (0.99) in our model despite the high uncertainty of RCT data.</p> <p>In this case study we identified major challenges related to the identification of relevant benefit-risk criteria and taking into account the diversity and quality of evidence available to inform the benefit-risk assessment.</p> <p>Conclusion The main challenges in applying formal methods for medical benefit-risk assessment for a marketed drug are related to outcome definitions and data availability. Data exists from many different sources (both randomised clinical trials and observational studies) and the variability in the studies is large.</p>

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Benefit-risk assessment in a post-market setting: A case study integrating real-life experience into benefit-risk methodology

Running head (50 chars): Benefit-Risk Assessment in a Post-Market Setting

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- The descriptive framework BRAT provides a good contextual basis and transparency for benefit-risk assessment of an older product with long established use such as warfarin.
 - Defining benefit-risk criteria and identifying data sources were found to be iterative where the two steps inform each other.

- Data availability, quality, consistency in reporting and changing safety requirements over the years were the greatest limitations when assessing benefit-risk balance of older medicinal products.
- The quantitative method stochastic multi-criteria acceptability analysis (SMAA) handles uncertainty in data and value preferences, and so allows exploration of their impact on benefit-risk balance.

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Abstract Words (250/250)**Purpose**

Difficulties may be encountered when undertaking a benefit-risk assessment for an older product with well-established use but with a benefit-risk balance that may have changed over time. This case study investigates this specific situation by applying a formal benefit-risk framework to assess the benefit-risk balance of warfarin for primary prevention of patients with atrial fibrillation.

Methods

We used the qualitative framework BRAT as the starting point of the benefit-risk analysis, bringing together the relevant available evidence. We explored the use of a quantitative method (Stochastic Multi-criteria Acceptability Analysis - SMAA) to demonstrate how uncertainties and preferences on multiple criteria can be integrated into a single measure to reduce cognitive burden and increase transparency in decision-making.

Results

Our benefit-risk model found that warfarin is favourable compared to placebo for the primary prevention of stroke in patients with atrial fibrillation. This favourable benefit-risk balance is fairly robust to differences in preferences. The probability of a favourable benefit-risk for warfarin against placebo is high (0.99) in our model despite the high uncertainty of RCT data.

In this case study we identified major challenges related to the identification of relevant benefit-risk criteria and taking into account the diversity and quality of evidence available to inform the benefit-risk assessment.

Conclusion

The main challenges in applying formal methods for medical benefit-risk assessment for a marketed drug are related to outcome definitions and data availability. Data exists from many different sources (both randomised clinical trials and observational studies) and the variability in the studies is large.

For Review Only

Introduction

There is increased interest from regulatory agencies in applying structured benefit-risk (BR) assessment throughout the life-cycle of a medicinal product,¹ as expressed in the European Medicines Agency (EMA) roadmap to 2012, the recent EU pharmacovigilance legislation, and the U.S. Food and Drug Administration (FDA) Prescription Drug User Fee Act (PDUFA V).

Formal qualitative and quantitative BR methodologies have been applied to BR assessments of medicines but are mainly focused on newer products.¹ BR assessment of older medicines poses some different challenges. We tested the applicability of a formal BR framework to a case study of an older medicine, warfarin, for the primary prevention of stroke in patients with atrial fibrillation. Warfarin has been marketed since 1954 and is one of the most commonly used oral anticoagulant in North America and Europe. It has established efficacy for the prevention of thromboembolic events in patients with atrial fibrillation, but also has well-known adverse events such as haemorrhage (bleeding) and a number of drug interactions.²

This case study, undertaking a BR assessment for an older medicine was conducted to identify which specific challenges might exist for medicines in this category.

Methods

A recent review of methodologies for medical BR decision-making was conducted by Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) Work Package 5 (WP5). Thirteen BR methods were recommended for testing in real-life BR assessment.³ The WP5's methodology review argued that *descriptive frameworks* do not necessarily perform quantitative BR assessments *per se*, but do provide a structured approach to framing the problem with the intention of clearly establishing the decision context and ensuring transparency.³ For this case study we used the BRAT framework^{3, 4} as a basis for the BR analysis of warfarin for stroke prevention in patients with atrial fibrillation.

The assessment was conducted in three stages. The first stage of the benefit-risk assessment compared warfarin to placebo. Data from randomised clinical trials (RCTs) for the primary prevention of stroke in patients with atrial fibrillation were used in the BR analysis.⁵⁻⁹

The qualitative analysis was complemented with the quantitative method Stochastic Multi-criteria Acceptability Analysis (SMAA).^{3, 10, 11} SMAA provides a way to explore the robustness of a BR decision in relation to uncertainty in both the actual clinical data as well as different stakeholder preferences.

Decision context

The decision context determines the focus of a BR assessment. In this case study we focused on the following decision contexts:

- Based on the RCT data for warfarin versus placebo/no treatment for primary stroke prevention in patients with atrial fibrillation, is the BR balance in favour of warfarin?

- Based on available observational data for treatment with warfarin for primary stroke prevention in patients with atrial fibrillation, is there evidence that affects the BR balance of warfarin?
- Has newer RCT for primary stroke prevention in patients with atrial fibrillation changed the BR balance of warfarin compared to placebo?

Identify outcome

During a face-to-face brainstorm session we discussed the outcomes for the BR assessment and constructed the initial value tree. This tree was refined in several steps, due to data availability (data to inform each criterion) and to ensure the minimization of double-counting, the final value tree is shown in figure 1. This process was iterative – the BRAT steps to ‘identify outcome’ and ‘identify data sources’ were revisited several times. For a more in-depth description of the process see Appendix 2.

Identify data sources

A systematic literature search was conducted for reviews and/or meta-analyses of RCTs comparing warfarin versus placebo for the primary prevention of stroke in patients with atrial fibrillation. One reviewer (CEH) examined titles and abstracts of identified reviews, and obtained and assessed relevant articles in full. Reference lists of selected reviews were examined. For a more through description see Appendix 1

We identified 37 review articles from which six relevant RCTs were identified,^{5-9, 12}, one of which was excluded because it studied secondary rather than primary prevention.¹². In addition, seven observational studies were also identified,¹³⁻¹⁹ although it was not designed for this purpose. This was considered sufficient for investigating the

difficulties that may be encountered with undertaking a BR assessment for an older product with well-established use. The studies were used to compare results from RCTs to actual practice. An overview of data sources used can be found in Appendix 3.

In the initial value tree we identified criteria relevant for the BR assessment. However, the definitions of the criteria were inconsistent and dependent on the outcomes available in the data sources. To accommodate the differences in outcome definitions across the five studies, the criteria were re-defined as shown in table 1.

(TABLE 1 HERE)

Customise BR framework

To minimise the decision problem to a purely medical one, the risk category of inconvenience was excluded in the customised framework.

Assess outcome importance

Several tools exist to assess outcome importance, and the BRAT framework does not specify any method. The first assessment of outcome importance was for defining and customising the value tree, and thereby selecting only the relevant BR criteria. For this analysis the BR criteria were rank ordered according to utility (a subjective measure that describes preferences such as satisfaction and risk attitude for an outcome). The order was based on the disutility value (opposite of utility i.e. describes the avoidance towards an outcome) for the criteria given in the Pink 2012 study²⁰. Table 2 gives the rank order of the criteria with the top being of the highest importance and the bottom of the least importance.

(TABLE 2 HERE)

Quantify and interpret key benefit-risk metrics

The incidence risk difference and the 95% confidence interval are displayed for each criterion in the BR assessment, both in numerical form and visually in a forest plot (see figure 2). The criteria are ordered according to the ranking in the above section, from the top, with ‘all-cause mortality’ as the most important criterion.

Exploring the BR balance using SMAA

The criterion “Major Haemorrhage” was not consistently defined across studies, and events may or may not be disabling. Consequently preferences assigned to the criterion may have greater uncertainty. The SMAA analysis can give a better understanding of the impact of different preferences and their uncertainties on the BR balance. Two different weight scenarios were explored:

Scenario A: The weight on each criterion corresponds to the disutility assigned in the Pink paper from 2012.²⁰ The criteria “All-cause Mortality” was not reported in the Pink 2012 analysis and for this scenario we assumed a value of 0.4.

Scenario B: Criteria “Disabling Ischaemic Stroke” and “Major Haemorrhage” were assumed to carry the same weight. This is equivalent to assuming all “Major Haemorrhage” events are disabling.

Since the weights from the literature disregard value functions for individual disutility, they implicitly account for both weights and utilities. The value functions and data to be used in our SMAA model may be different from the ones accounted for in the literature, and therefore we needed to ‘normalise’ the disutility values so that the total adds up to 1. This ensured that the weights and utilities in the final SMAA model match the ones from the literature. To further explore the typical preference profile of a decision-maker in relation to

the two treatment options (warfarin and placebo), we conducted an analysis using missing weights assuming that these weights are uniformly distributed between values of 0 and 1. Scenario W and C for favouring warfarin and favouring placebo, respectively.

Normalising weights for use in SMAA model

Scenario A: The normalised disutility values that act as a constraint to the SMAA model are given in table 3.

(TABLE 3 HERE)

We then calculated 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 $w_i (i = 1, 2, 3, \dots, n)$ 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:

$$\begin{aligned} \text{Overall BR score} = & (\text{'All-cause Mortality'}) + (0.58 \times \text{'Disabling Ischaemic Stroke'}) \\ & + (0.35 \times \text{'Major Haemorrhage'}) + (0.35 \times \text{'Non-disabling Ischaemic Stroke'}) \\ & + (0.15 \times \text{'Minor Haemorrhage'}) \end{aligned}$$

Scenario B: The normalised disutility values that act as a constraint to the SMAA model are given in table 4.

(TABLE 4 HERE)

As previously described for scenario A

$$\begin{aligned}\text{Overall BR score} = & (\text{'All-cause Mortality'}) + (0.58 \times \text{'Disabling Ischaemic Stroke'}) \\ & + (0.58 \times \text{'Major Haemorrhage'}) + (0.35 \times \text{'Non-disabling Ischaemic Stroke'}) \\ & + (0.15 \times \text{'Minor Haemorrhage'})\end{aligned}$$

Evidence from observational studies and newer RCTs

In the second stage it was assessed whether the warfarin RCT data are compatible with data from current clinical practice studies (observational studies) in an attempt to include the real life experience¹³⁻¹⁹ by comparing study populations, comparative treatments, and treatment effects of warfarin between observational studies and RCTs.

In the third stage, changes in the BR profile over time were considered through data from three recent comparative clinical trial programs for the new oral anticoagulants.²¹⁻²³ We assessed whether warfarin data from these new trials were comparable to the original data by comparing the outcome in the warfarin arm of the newer RCTs to the older RCTs.

Results

The final value tree includes the criteria considered appropriate for the assessment, without problems of double-counting and with data to support each criterion.

(FIGURE 1 HERE)

The data summary table (table 5) provides the effect of warfarin versus placebo on each criterion. The benefit and risk are also quantified in the forest plot, figure 2.

(TABLE 5 HERE)

(FIGURE 2 HERE)

In figure 3 the result of the SMAA analysis is shown. Both models in scenario A and scenario B show high probabilities (both 0.99) of warfarin having a favourable BR balance compared to placebo. In the missing weights analysis, we determined whether the central weights considered placebo to be more favourable than warfarin (scenario C). The analysis shows that the weight of 'Major Haemorrhage' has to be around five times the weight of each of the other four criteria, including 'All-cause Mortality' for warfarin to have an unfavourable BR balance compared to placebo.

(FIGURE 3 HERE)

For the comparison between RCTs and observational studies, and warfarin versus newer anticoagulants, the criteria are defined differently than in the value tree (figure 1) to accommodate available data. Data are shown in Appendices 3 and 4.

There is a discrepancy between the study population and treatment in the RCTs and in actual practice (defined in observational studies). The difference in target INR and time in target range (TTR) between RCTs and observational studies is shown in figure 4, and study population characteristics in table 6.

(FIGURE 4 HERE)

(TABLE 6 HERE)

The outcomes from the observational studies are compared to the outcome from the RCTs, (see figure 5). In order to compare data from observational studies with data from RCTs, the benefit criteria 'disabling' and 'non-disabling' ischaemic stroke had to be grouped, since it was not possible to distinguish between the two types of events in the observational studies.

(FIGURE 5 HERE)

The three newer RCTs, RELY^{22, 24, 25}, ROCKET-AF^{23, 26} and ARISTOTLE²¹ provide data from trials run to current standards both on warfarin and the new products, and allow for the comparison of old and new clinical trial data (see figure 6). The BR outcomes used for comparison between old and new RCTs data were chosen to mimic the criteria from the defined value tree. However, it was not possible to extract the data for comparison that matched the initial defined criteria completely.

(FIGURE 6 HERE)

Discussion

Based on data from the five RCTs on warfarin versus placebo, our BR model suggests that warfarin has a favourable BR balance compared to placebo for the primary prevention of stroke in atrial fibrillation, see figure 2.

Although in this case study a choice was made to assign weights based on published disutility values, this step in the BR assessment was subject to some discussion regarding risk aversions. This refers especially to the criterion 'Major Haemorrhage' which is defined as CNS haemorrhage or level of medical intervention, but could clearly also include events that are permanently disabling. These possible disabling events were expected to be associated with the same risk aversion as the criterion 'Disabling Ischaemic Stroke'.

The different weight scenarios explored using the SMAA model suggest that the favourable benefit-risk balance of warfarin is fairly robust to difference in preferences (see figure 7); and that the probability of a favourable benefit-risk balance for warfarin against placebo is high despite the high uncertainty in the RCT data, given our model.

We considered that the 'Inconvenience' criteria should only be taken into account after the BR assessment for the drug and its comparator is done based on pharmacological properties. A borderline negative BR balance might be improperly shifted to positive if the assessment was based only on inconvenience criterion. There are other situations where it would be appropriate to include convenience criteria, e.g. in the BR decision taken by an individual patient.

Our comparison of study population characteristics suggests that age could be a source of bias, since the actual practice population is older than the RCT population (table 6). Also there is a better control of treatment in the RCTs than in actual practice defined by time

in target INR (TTR) (see figure 4), which might influence the BR balance of warfarin. When we compare the effect of warfarin treatment between observational studies and RCTs, there seems to be a good agreement between the evidence at least on the criteria 'All-cause Mortality' and 'Major Haemorrhage', while the effect on the criteria 'Ischaemic Stroke' shows better results of warfarin in the RCTs. In this context it should be mentioned that the observational studies included in this case study cannot be considered exhaustive.

There is a good agreement between the evidence from the older and newer RCTs, in the four criteria 'All-cause Mortality', 'Ischaemic Stroke (fatal and non-fatal)', 'Intracranial Haemorrhage' and 'Extracranial Haemorrhage'. However, there are differences between the old and the new RCTs in relation to target INR (which is generally narrower in the new trials) and TTR (which is general lower in the new RCTs compared to the older ones).

This warfarin case study, undertaking a BR assessment for an older medicine, was conducted to identify which specific challenges might exist for medicines in this category, often widely used, and where the clinical study evidence base may well be before the Good Clinical Practice (GCP) era.

The BRAT framework provides a good contextual basis for the BR assessment of an older product. The framework ensures that the process is documented, and that the discussions are focused on outcomes relevant to the BR problem. This ensures the results of the BR assessment are robust and the decisions made are relevant to the population who are affected by the use of these products.

The experience from this case study shows that the BRAT steps of defining BR criteria and identifying data sources are strongly iterative processes where the two steps inform each other in a circular or parallel manner, rather than linearly.

One of the major challenges relates to the identification of relevant BR criteria and the ability to handle the evidence available to inform the BR assessment. The outcomes from the literature are often not negotiable. They should be assessed for relevance, compatibility and applicability. For example, it was necessary to use overlapping endpoints that were not identical across studies. And the reliance on studies designed for different purposes meant that criteria had wide definitions and may conflict each other.

The structured approach for older medicines should account for the context of the quality of evidence available on these medicines, in particular old clinical trial data that are likely to be less robust (according to current GCP standards). In the warfarin case study we identified RCT data in the indication of atrial fibrillation, including three relatively new studies in which standard of care (i.e. warfarin) was used as the comparator.²¹⁻²³ These studies provide clinical trial data to current standards on warfarin, as well as the newer products, and allowed for the comparison of older clinical trial data with the new data, derived from the assessment reports for European Marketing Authorisations. For older products the results would be based on limited data, with uncertainty on the external validity and generalizability compared to more recent medical practice.

The limitations of the available/obtainable data for older products affect the development of the value tree, which means that there may be very relevant criteria for which there is no data, or only limited or unusable data are available, e.g. 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.²⁷ This may lead to 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 might have played a major role in the BR assessment if data had been available (e.g.

disabling bleeding events). There may also be an asymmetric aversion to risk (for example different aversions to haemorrhagic, versus ischaemic stroke). As it is important to avoid inconsistencies between conclusions of identical but differently framed decision problems, it may be helpful to reason in terms of health outcomes, like mortality and disability, rather than focusing on the cause of events.

The impact of missing data on the value tree and consequent BR decision may depend on the BR model used. When aggregating data from different sources it is important to note issues such as different definitions of outcomes, different way of measuring certain effects and bias when combining data. This can necessitate data transformation or even criteria customization. However, more qualitative use of the BRAT framework will allow the user to incorporate some degree of flexibility. For SMAA, this is less a problem as the model can accommodate all types and format of data.

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Table 1: Criteria definitions

Criteria	Definition
Disabling Ischaemic Stroke	Disabling with or without loss of independent function (non-fatal)
Non-disabling Ischaemic Stroke	Little or no disability a month after the event
Major Haemorrhage	CNS or requiring medical intervention (non-fatal)
Minor Haemorrhage	Other bleeding events

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Table 2: Rank ordering of criteria, based on disutility values stated in the Pink 2012 paper²⁰.

Outcome	Importance	Disutility Pink2012
All-cause Mortality	High	
Disabling Ischaemic Stroke		0.233
Major Haemorrhage		0.1385
Non-disabling Ischaemic Stroke		0.1385
Minor Haemorrhage	Low	0.06

Table 3: Overview of the weights on the five criteria for scenario A. The criteria are weighted according to Pink 2012²⁰ 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	Normalised*
All-cause Mortality	Highest	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	Lowest	0.06	0.06

† Not from Pink2012

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

Table 4: Overview of the weights on the five criteria for scenario B. The criteria weights are based on Pink 2012 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	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	0.056

† Not from Pink2012

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

Table 5: Data summary table data from RCTs (only direct comparison warfarin versus control (placebo blinded and un-blinded) primary prevention of stroke, atrial fibrillation.

Category		Criteria	Warfarin versus control	
			Risk difference per 1000 per year (95% CI)	Log peto odds ratio (95% CI)
Benefit	Reduction in all-cause mortality	All-cause mortality	-14.7 (-28.58, -0.82)	-0.36 (-0.70, -0.07)
	Reduction in ischaemic stroke	Disabling ischaemic stroke ^{A *}	-12.54 (-20.56, -4.52)	-0.97 (-1.58, -0.36)
		Non-disabling ischaemic stroke ^{B *}	2.88 (-2.42, 8.17)	-1.53 (-2.23, -0.83)
Risk	Increase in haemorrhage	Major Haemorrhage ^C	-12.95 (-19.34, -6.55)	0.26 (-0.38, 0.93)
		Minor Haemorrhage ^{D *†}	44.98 (28.52, 61.45)	0.76 (0.40, 1.08)

Data polled from AFASAK, BAATAF, CAFA, SPINAF & SPAF.

* CAFA study not included, † SPAF study not included

^A Disabling both with and without loss of independent function (non-fatal)

^B Leaving little or non-definite functional disability a month after onset

^C Requiring medical intervention also including CNS haemorrhage (non-fatal)

^D All other

Table 6: Characteristics of study population in older RCTs newer RCTs, and observational studies.

Study	Age, years	Gender, male, %	Prior stroke, %	Diabetes, %	Hypertension, %	Heart Failure, %	Angina, %
Gottlieb1994 ¹⁸	87,7	66	27	26	53	42	24
Caro1999 ¹⁷	70,8	66	21	24	43	34	21
Kalra2000 ¹⁵	77	40	14	15	43	20	NA
Go2003 ¹³	71	59,2	10,9	18,2	51,6	33,1	NA
Darkow2005 ¹⁶	79,8	45,5	6,2	17,3	37,1	NA	NA
Hylek2007(<80) ¹⁹	73	57	3	19	71	23	NA
Hylek2007(>80) ¹⁹	84	45	9	24	83	37	NA
Jacobs2009 ¹⁴	82	22	NA	NA	NA	NA	NA
ARISTOTLE ²¹	70	65	19,7	24,9	87,3	35,4	NA
RE-LY ²⁴	71,6	63,3	19,8	23,4	78,9	31,9	NA
ROCKET-AF ²⁶	NA	60,3	54,6	39,5	90,8	62,3	NA
AFASAK I ⁵	NA	53	5	7	32	50	19
BAATAF ⁸	68,5	75	3	14	51	24	23
CAFA ⁶	68	75,9	3,2	13,9	43,3	23,5	21,9
SPAF I ⁷	64	74	8	12	49	NA	NA
SPINAF I ⁹	67	100	NA	17	55	31	22

Figure 1: Value-tree for the BR assessment of warfarin versus placebo in atrial fibrillation. The BR consists of favourable effects and unfavourable effects; each is split up in categories, which are split up in outcomes.

Figure 2: Forest plot, showing the incidence risk difference for warfarin versus control on each BR criteria. The criteria are placed based on rank order, with the criteria of highest importance in the top.

Figure 3: To the left the normalised weights of the criteria for each scenario is shown, scenario (W) corresponds to the central weights for favouring warfarin, and the (C) for favouring placebo, in the missing weigh analysis. To the right the probability of warfarin having a favourable BR compared to placebo is shown for each weight scenario.

Figure 4: Target INR (to the left) and Time in target INR (to the right) for older and newer RCTs and observational studies.

Figure 5: Comparing RCTs for warfarin versus placebo (control) and observational studies for warfarin versus no-treatment (control), in a forest plot. Each criterion is shown separately with each bar representing observational study or a pooled estimate for the 5 RCTs. The criteria 'All Ischaemic Stroke' and 'Major Haemorrhage' include both fatal and non-fatal events.

Figure 6: Point estimates and 95%CI interval of the event rate of warfarin (events per 1000 patients per year) for the outcomes 'All-Cause Mortality', 'Ischaemic Stroke', 'Intracranial Haemorrhage' and 'Extracranial Haemorrhage' from the three newer RCTs and 5 older RCTs (* fatal/non-fatal, ¹ incl. unspecified stroke, ² Major extracranial haemorrhage).

Appendix 1: Literature Search

We searched on following electronic databases:

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

The search was 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 was limited by language English.

Reference lists of all relevant papers were screened to identify other potentially relevant articles.

Scopus 2012.06.13	Medline 2012.06.14	Cochrane 2012.06.14
TITLE-ABS-KEY(warfarin OR coumadin OR jantoven OR marevan OR lawarin OR waran OR warfant) AND (TITLE-ABS-KEY("atrial fibrillation" OR "atrium fibrillation" OR "auricular fibrillation" OR "heart fibrillation" OR "cardiac fibrillation") AND NOT (TITLE-ABS-KEY(rivaroxaban OR dabigatran OR apixaban) AND (TITLE-ABS-KEY("systematic review" OR	(((((warfarin[Title/Abstract]) OR coumadin[Title/Abstract]) OR jantoven[Title/Abstract]) OR marevan[Title/Abstract]) OR lawarin[Title/Abstract]) OR waran[Title/Abstract]) OR warfant[Title/Abstract] AND atrial fibrillation[Title/Abstract] AND (systematic review[Title/Abstract]) OR meta-analysis[Title/Abstract] NOT ((rivaroxaban[Title/Abstract]) OR dabigatran[Title/Abstract]) OR	warfarin in Title, Abstract or Keywords and atrial fibrillation in Title, Abstract or Keywords

Appendix 2: Iterative process of identifying outcomes and data sources

The initial value tree was constructed based on discussions/brain-storm in a face-to-face meeting on 30th 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 1). 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 1: 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, BAATAF, CAFA, SPIN I and SPINAF and EAFT). (1-6) The Cochrane review by Aguilar and Hart (7) included endpoints which could best fit our benefit-risk criteria defined in the initial 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 1: Data source table, identified endpoints and definitions

	Category	Endpoint	Definition	Study Type
Benefit		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 (7)

	Reduction in Ischaemic stroke	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 (7)
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 (7)
		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 (7)

The criteria ‘all-cause mortality’ was included since it was felt that fatal events should be considered separately, 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 **Error! Reference source not found.** 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.

Figure 2: Customised initial value-tree for the benefit-risk assessment of warfarin versus placebo.

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 criterion 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 BR of drug/comparators has been made based on its medical/pharmacological properties only. This is because a borderline negative BR 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

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4 with warfarin and placebo/no treatment for primary prevention of stroke in atrial fibrillation was
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6 identified.(1-5) The table below shows the possible relevant endpoints identified in the 5 RCTs, and
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8 a grouping of endpoints to be used, explains the proposed modifications of the value tree criteria.
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Table 2: 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	
	Fatal ischaemic stroke	Disabling ischaemic stroke	Non-disabling ischaemic stroke	Minor ischaemic stroke	Fatal bleed	Major bleed
AFASAK	Fatal ischaemic stroke	Definite functional disability a month after event	Not leaving definite functional disability a month after onset	stroke		Requiring medical intervention
				Other		
BAATAF	Fatal ischaemic stroke	Severe ischaemic stroke	Moderate ischaemic stroke	Mild ischaemic stroke		Major bleed
		Deficits that preclude independent functioning	Substantial deficit but with independent function	Little of no persistent deficit		Intracranial, fatal or bleeding leading to transfusion of four or more unit of blood within 48 hours*^
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
						Minor bleed
						Other bleeding events

SPINAF	Fatal Cerebral infraction	Cerebral infraction with major impairment	Cerebral infraction with minor impairment	Cerebral infraction with no impairment	Fatal	Major Bleed Required blood transfusion, emergency procedure or admission to an intensive care unit ^	Minor Bleed Other bleeding events
		Independence lost at 30 day after the event	Independence at 30 days after the event, despite impairment	No impairment at 30 days after the event			

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

Figure 3: Value tree number 1 of second iteration

Table 3: 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 (8)
	Reduction in ischaemic stroke	Major stroke	Disability with or without independent function a month after event (non-fatal)	AFASAK (1)
				BAATAF (2)
				SPINAF (5)
				SPAF (4)
		Minor stroke	Non-disabling a month after event (non-fatal)	AFASAK (1)
				BAATAF (2)
				SPINAF (5)
Risk	Increase in haemorrhage	Major haemorrhage	Requiring medical intervention or CNS haemorrhage (non-fatal)	AFASAK (1)
				BAATAF (2)
				CAFA(3)
				SPINAF (5)
				SPAF (4)
		Minor haemorrhage	Other bleeding events (non-fatal)	AFASAK (1)
				BAATAF (2)
				CAFA (3)
				SPINAF (5)

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

Figure 4: Value tree number 2 of second iteration

Table 4: Data source table corresponding to value tree number 2

	Category	Outcome		Study
Benefits	Reduction in ischaemic stroke	Fatal ischaemic stroke		AFASAK (1)
				BAATAF (2)
				SPINAF (5)
				SPAF (4)
	Disabling ischaemic stroke	Disability with or without independent function a month after event (non-fatal)		AFASAK (1)
				BAATAF (2)
				SPINAF (5)
				SPAF (4)
	Non-disabling ischaemic stroke	Non-disabling a month after event (non-fatal)		AFASAK (1)
				BAATAF (2)
				SPINAF (5)
				SPAF (4)
Risk	Increase in haemorrhage	Fatal haemorrhage		AFASAK (1)
				BAATAF (2)
				CAFA (3)
				SPINAF (5)
				SPAF (4)
	Major haemorrhage	Requiring medical intervention or CNS haemorrhage (non-fatal)		AFASAK (1)
				BAATAF (2)
				CAFA (3)
				SPINAF (5)
				SPAF (4)
	Minor haemorrhage	Other bleeding events (non-fatal)		SPINAF (5)
				SPAF (4)
				SPINAF (5)

Value tree number 1 and 2 are quite similar 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 number 3 with corresponding data source table (same comment as above regarding convenience criteria)

Figure 5: Value tree number 3 (second iteration)

Table 5: Data source table corresponding to value tree number 3

	Category	Outcome		Study
Benefits	Reduction in ischaemic stroke	Fatal ischaemic stroke		AFASAK
				BAATAF
				SPINAF
				SPAF
		Disabling ischaemic stroke	Disability with or without independent function a month after event (non-fatal)	AFASAK
				BAATAF
				SPINAF
				SPAF
		Non-disabling 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 includes 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 BR of drug/comparators has been made based only on its pharmacological properties, because a border-line negative BR 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 BR balance assessment.

Appendix 3: Data source tables

Outcome	Study	Study type	Comparator	Mean follow-up, years	Warfarin		Comparator		Rate % per year
					cases	total	cases	total	Rate % per year
All-cause mortality	AFASAK I (7)	RCT	placebo (un-blinded)	1.2	20	335	28	336	-
	BAATAF (7)	RCT	placebo (un-blinded)	2.2	11	212	26	208	-
	CAFA (7)	RCT	placebo (blinded)	1.3	10	187	8	191	-
	SPAF I (7)	RCT	placebo (un-blinded)	1.2	6	210	8	211	-
	SPINAF(7)	RCT	placebo (blinded)	1.7	22	281	29	290	-
	ARISTOTLE(9)	RCT	Apixaban	1.8	603	9120	669	9081	3.94
	ROCKET-AF (10)	RCT	Rivaroxaban	1.9	621	7081	667	7090	4.92
	RE-LY (11)	RCT	Dabigatran, 110mg	2.0	446	6015	487	6022	4.13
	RE-LY (11)	RCT	Dabigatran, 150mg	2.0	438	6076	487	6022	4.13
	Jacobs2009 (12)	Obs	NA	-	18	90	-	-	-
Ischaemic stroke (fatal/non-fatal)	Go2003 (13)	Obs	No-treatment	-	-	6320	-	5089	5.33
	AFASAK I (1)	RCT	placebo (un-blinded)	1.2	6	315	17	315	-
	BAATAF (2)	RCT	placebo (un-blinded)	2.2	3	205	11	201	-
	CAFA (3)	RCT	placebo (blinded)	1.3	6	181	9	184	-
	SPAF I (4)	RCT	placebo (un-blinded)	1.2	7	193	15	194	-
	SPINAF (5)	RCT	placebo (blinded)	1.7	5	260	19	265	-
	ARISTOTLE(9)	RCT	Apixaban	1.8	175	9081	162	9120	0.97
	ROCKET-AF (10)	RCT	Rivaroxaban	-	161	7082	149	7061	1.34
	RE-LY (11)	RCT	Dabigatran 110mg	2	142	6022	159	6015	1.34
	RE-LY (11)	RCT	Dabigatran 150mg	2	142	6022	111	6076	0.92
Disabling ischaemic stroke (non-fatal)	Kalra2000 (14)	Obs	NA	2	6	77	NA	NA	NA
	Gottlieb1994 (15)	Obs	NA	-	4	140	NA	NA	NA
	Go2003 (13)	Obs	No-treatment	-	141	6320	231	5089	1.88
	Darkow2004 (16)	Obs	No-treatment	2	183	4895	341	7644	2.83
	AFASAK I (1)	RCT	placebo (un-blinded)	1.2	4	335	7	336	-
	BAATAF (2)	RCT	placebo (un-blinded)	2.2	2	212	8	208	-
	SPAF I (4)	RCT	placebo (un-blinded)	1.2	2	210	7	211	-

	SPINAF (5)	RCT	placebo (blinded)	1.7	3	260	-	9	265	-
Non-disabling ischaemic stroke	AFASAK I (1)	RCT	placebo (un-blinded)	1.2	0	335	-	5	336	-
	BAAATAF (2)	RCT	placebo (un-blinded)	2.2	0	212	-	4	208	-
	SPAF I (4)	RCT	placebo (un-blinded)	1.2	4	210	-	10	211	-
	SPINAF (5)	RCT	placebo (blinded)	1.7	0	260	-	9	265	-
	AFASAK I (1)	RCT	placebo (un-blinded)	1.2	0	315	-	0	315	-
Major haemorrhage (fatal, CNS or requiring medical intervention)	BAAATAF (2)	RCT	placebo (un-blinded)	2.2	8	205	-	8	201	-
	CAFA (3)	RCT	placebo (blinded)	1.3	5	181	-	2	184	-
	SPAF I (4)	RCT	placebo (un-blinded)	1.2	4	193	-	4	194	-
	SPINAF (5)	RCT	placebo (blinded)	1.7	7	260	-	4	265	-
	Kalra2000 (14)	Obs	NA	-	4	77	1.4	NA	NA	NA
	Hylek<80 (17)	Obs	NA	1	12	319	4.75	NA	NA	NA
	Hylek>80 (17)	Obs	NA	1	14	153	13.08	NA	NA	NA
	Gottlieb1994 (15)	Obs	NA	-	2	140	0.65	NA	NA	NA
	Darkow2005 (16)	Obs	No-treatment	2	217	4895	2.68	372	7644	3.1
	Caro1999 (18)	Obs	No-treatment	-	4	87	NA	1	38	NA
Intracranial haemorrhage (fatal/non-fatal)	Go2003 (13)	Obs	No-treatment	-	19	6320	0.15	11	5089	0.09
	AFASAK I (1)	RCT	placebo (un-blinded)	1.2	0	315	-	0	315	-
	BAAATAF (2)	RCT	placebo (un-blinded)	2.2	1	205	-	0	201	-
	CAFA (3)	RCT	placebo (blinded)	1.3	1	181	-	0	184	-
	SPAF I (4)	RCT	placebo (un-blinded)	1.2	2	193	-	2	194	-
	SPINAF (5)	RCT	placebo (blinded)	1.7	1	260	-	0	265	-
	ARISTOTLE(9)	RCT	Apixaban	1.8	122	9052	0.8	52	9088	0.33
	ROCKET-AF (10)	RCT	Rivaroxaban	-	84	7125	0.7	55	7111	0.5
	RE-LY (11)	RCT	Dabigatran 110mg	2	87	6022	0.74	27	6015	0.23
	RE-LY (11)	RCT	Dabigatran 150mg	2	87	6022	0.74	36	6076	0.3
Extracranial haemorrhage (fatal/non-fatal)	AFASAK I (1)	RCT	placebo (un-blinded)	1.2	0	315	-	0	315	-
	BAAATAF (2)	RCT	placebo (un-blinded)	2.2	7	205	-	8	201	-
	CAFA (3)	RCT	placebo (blinded)	1.3	4	181	-	2	184	-
	SPAF I (4)	RCT	placebo (un-blinded)	1.2	2	193	-	2	194	-
	SPINAF (5)	RCT	placebo (blinded)	1.7	6	260	-	4	265	-
	RE-LY (11)	RCT	Dabigatran 110mg	2	315	6022	2.67	299	6015	2.51
	RE-LY (11)	RCT	Dabigatran 150mg	2	315	6022	2.67	342	6076	2.84
	ARISTOTLE(9)	RCT	Apixaban		340	9052	2.27	275	9088	1.79
	AFASAK I (1)	RCT	placebo (un-blinded)	1.2	20	335	-	0	336	-
		RCT								
Minor										

haemorrhage (not - fatal, CNS or requiring medical intervention)	BAATAF (2)	RCT	placebo (un-blinded)	2.2	32	212	-	14	208	-
	CAFA (3)	RCT	placebo (blinded)	1.3	-	-	-	-	-	-
	SPAF I (4)	RCT	placebo (un-blinded)	1.2	-	-	-	-	-	-
	SPINAF (5)	RCT	placebo (blinded)	1.7	64	260	-	46	265	-
	Kalra2000 (14)	Obs	NA	2	16	77	5.4	-	-	-
	Gottlieb1994 (15)	Obs	NA	-	36	140	11.69	-	-	-

¹ Incl. unspecified stroke² Major extracranial haemorrhage

Outcome	Study	Risk rate, events per 1000 patients per year (95%CI)	Warfarin	Warfarin versus control *	Risk difference, events per 1000 patients per year (95%CI)	Pooled RCTs
All-cause mortality	SPINAF	46.05	(30.75, 68.05)	-12.77	(-40.61, 15.10)	-14.7 (-28.58, -0.82)
	SPAF I	23.81	(10.97, 50.77)	-7.79	(-38.09, 23.39)	
	CAFA	41.14	(22.54, 73.56)	8.92	(-26.38, 43.30)	
	BAATAF	23.58	(13.28, 41.14)	-33.23	(-57.81, -7.77)	
	AFASAK I	49.75	(32.48, 75.34)	-19.69	(-52.52, 13.56)	
	Go2003	44.60	-	-8.70	-	-
	Jacobs2009	200.00	(130.42, 294.14)	-	-	-
	ARISTOTLE	39.40	(36.62, 42.37)	-	-	-
	RELY	41.26	(37.88, 44.91)	-	-	-
Ischaemic Stroke (fatal/non-fatal)	ROCKET-AF	49.25	(45.81, 52.93)	-	-	-
	SPINAF	9.05	(3.53, 22.87)	-33.13	(-53.23, -10.86)	-25.56 (-35.72, -15.39)
	SPAF I	21.59	(9.26, 49.34)	-34.25	(-69.62, 3.72)	
	CAFA	21.25	(9.12, 48.48)	-16.38	(-48.06, 16.78)	
	BAATAF	4.43	(1.22, 15.85)	-20.44	(-35.87, -2.34)	
	AFASKA I	15.87	(7.30, 34.11)	-29.10	(-53.50, -2.67)	
	Darkow2004	22.52	(19.53, 25.95)	-5.71	(-10.15, -1.38)	-
	Go2003	11.10	(9.43, 13.06)	-7.74	(10.74, -4.68)	-
	Gottlieb1994	12.99	(5.08, 32.34)	-	-	-
	Kalra2000	19.98	(9.28, 40.96)	-	-	-
Major haemorrhage	ARISTOTLE	10.47	(9.04, 12.12)	-	-	-
	RELY	11.97	810.17, 14.07)	-	-	-
	ROCKET-AF	14.21	(12.20, 16.55)	-	-	-
	SPINAF	15.84	(7.71, 32.07)	6.96	(-9.53, 22.28)	1.19 (-3.33, 5.71)

(fatal, CNS or requiring medical intervention)	SPAF I	17.27	(6.74, 43.39)	0.09	(-26.84, 26.93)		
	CAFA	21.25	(9.12, 48.48)	12.89	(-13.65, 36.42)		
	BAAATAF	17.74	(9.05, 34.14)	-0.35	(-18.58, 18.04)		
	AFASKA I	0.00	(0.00, 10.04)	0.00	(-8.46, 8.46)		
	Caro 1999	18.84	(7.39, 46.04)	10.99	(-16.25, 44.98)	-	-
	Darkow2005	26.87	(23.58, 30.58)	-4.13	(-8.89, 0.52)	-	-
	Gottlieb1994	6.49	(1.78, 22.99)	-	-	-	-
Minor haemorrhage (not - fatal, CNS or requiring medical intervention)	Hykel<80	47.62	(27.40, 81.76)	-	-	-	-
	Hykel>80	130.72	(78.99, 211.04)	-	-	-	-
	Kalra2000	14.00	(5.49, 33.99)	-	-	-	-
	Gottlieb1994	116.88	(87.23, 152.43)	-	-	-	-
	Kalra2000	53.97	(34.32, 80.83)	-	-	-	-
	SPINAF	144.80	(116.32, 177.62)	42.69	(1.98, 83.68)	-	-
	BAAATAF	68.61	(49.54, 93.33)	38.02	(10.64, 65.03)	-	-
Intracranial haemorrhage (fatal/non-fatal)	AFASAK I	49.75	(32.48, 75.34)	49.75	(24.90, 69.28)	-	-
	ARISTOTLE	8.02	(6.73, 9.56)	-	-	-	-
	RELY	7.41	(6.01, 9.12)	-	-	-	-
	ROCKET-AF	7.02	(5.67, 8.67)	-	-	-	-
	SPINAF	2.26	(0.12, 12.62)	-	-	-	-
	SPAF I	8.64	(2.37, 30.82)	-	-	-	-
	CAFA	4.25	(0.22, 23.56)	-	-	-	-
Extracranial haemorrhage (fatal/non-fatal)	BAAATAF	2.22	(0.11, 12.32)	-	-	-	-
	AFASKA I	0.00	(0.00, 10.04)	-	-	-	-
	ARISTOTLE	22.76	(20.51, 25.26)	-	-	-	-
	RELY	26.69	(23.96, 29.71)	-	-	-	-
	SPINAF	13.57	(6.25, 29.07)	-	-	-	-
	SPAF I	8.64	(2.37, 30.82)	-	-	-	-
	CAFA	17.00	(6.64, 42.64)	-	-	-	-
* Control, no treatment for observational studies, and placebo (blinded or un-blinded) for RCTs	BAAATAF	15.52	(7.56, 31.27)	-	-	-	-
	AFASKA I	0.00	(0.00, 10.04)	-	-	-	-
	ARISTOTLE	8.02	(6.73, 9.56)	-	-	-	-

Appendix 4: Data summary tables

Data summary table – Data from observational studies

	Outcome	Study	Warfarin Rate per 1000 patients per year (95%CI)		Warfarin versus control Risk difference per 1000 patients per year (95%CI)*	
Benefit	All-cause mortality	Go2003	44.60	NA	-8.70	NA
		Jacobs2009	200.00	(130.42, 294.14)	NA	NA
		SPINAF	46.05	(30.75, 68.05)	-12.77	(-40.61, 15.10)
		SPAF I	23.81	(10.97, 50.77)	-7.79	(-38.09, 23.39)
		CAFA	41.14	(22.54, 73.56)	8.92	(-26.38, 43.30)
		BAATAF	23.58	(13.28, 41.14)	-33.23	(-57.81, -7.77)
		AFASAK I	49.75	(32.48, 75.34)	-19.69	(-52.52, 13.56)
	Ischaemic Stroke (fatal/non-fatal)	Darkow2004	22.52	(19.53, 25.95)	-5.71	(-10.15, -1.38)
		Go2004	11.10	(9.43, 13.06)	-7.74	(10.74, -4.68)
		Gottlieb1994	12.99	(5.08, 32.34)	NA	
		Kalra2000	19.98	(9.28, 40.96)	NA	
		SPINAF	9.05	(3.53, 22.87)	-33.13	(-53.23, -10.86)
		SPAF I	21.59	(9.26, 49.34)	-34.25	(-69.62, 3.72)
		CAFA	21.25	(9.12, 48.48)	-16.38	(-48.06, 16.78)
		BAATAF	4.43	(1.22, 15.85)	-20.44	(-35.87, -2.34)
		AFASKA I	15.87	(7.30, 34.11)	-29.10	(-53.50, -2.67)
		Pooled RCT	NA		-25.56	(-35.72, -15.39)
Risk	Major haemorrhage (fatal/non-fatal)	Caro1999	18.84	(7.39, 46.04)	10.99	(-16.25, 44.98)
		Darkow2005	26.87	(23.58, 30.58)	-4.13	(-8.89, 0.52)
		Gottlieb1994	6.49	(1.78, 22.99)	NA	
		Hykel<80	47.62	(27.40, 81.76)	NA	
		Hylel>80	130.72	(78.99, 211.04)	NA	
		Kalra2000	14.00	(5.49, 33.99)	NA	
		SPINAF	15.84	(7.71, 32.07)	6.96	(-9.53, 22.28)
		SPAF I	17.27	(6.74, 43.39)	0.09	(-26.84, 26.93)
		CAFA	21.25	(9.12, 48.48)	12.89	(-13.65, 36.42)
		BAATAF	17.74	(9.05, 34.14)	-0.35	(-18.58, 18.04)
		AFASKA I	0.00	(0.00, 10.04)	0.00	(-8.46, 8.46)
		Pooled RCT	NA		1.19	(-3.33, 5.71)
	Major Haemorrhage (non-fatal)	Jacobs2009	55.56	(23.96, 123.54)	NA	
		SPINAF	15.84	(7.71, 32.07)	9.18	(-6.96, 23.68)
		SPAF I	11.90	(4.06, 34.29)	-3.89	(-27.10, 20.10)
		CAFA	12.34	(4.21, 35.46)	4.29	(-18.12, 25.18)
		BAATAF	15.01	(7.31, 30.26)	-0.29	(-17.00, 16.58)
		AFASAK I	2.49	(0.13, 13.93)	2.49	(-7.72, 10.58)
	Minor haemorrhage	Gottlieb1994	116.88	(87.23, 152.43)	NA	
		Kalra2000	53.97	(34.32, 80.83)	NA	
		SPINAF	144.80	(116.32, 177.62)	42.69	(1.98, 83.68)
		BAATAF	68.61	(49.54, 93.33)	38.02	(10.64, 65.03)
		AFASAK I	49.75	(32.48, 75.34)	49.75	(24.90, 69.28)

*Control, no treatment for observational studies, and placebo (blinded or un-blinded) for RCTs

Data summary table: newer RCTs

	Outcome	Study	Warfarin Event rate per 1000 patient per year (95%CI)	
Benefit	All-cause mortality	ARISTOTLE	39.40	(36.62, 42.37)
		RELY	41.26	(37.88, 44.91)
		ROCKET-AF	49.25	(45.81, 52.93)
		SPINAF	46.05	(30.75, 68.05)
		SPAF I	23.81	(10.97, 50.77)
		CAFA	41.14	(22.54, 73.56)
		BAATAF	23.58	(13.28, 41.14)
		AFASAK I	49.75	(32.48, 75.34)
	Ischaemic stroke (fatal/non-fatal)	ARISTOTLE ¹	10.47	(9.04, 12.12)
		RELY ¹	11.97	810.17, 14.07)
		ROCKET-AF	14.21	(12.20, 16.55)
		SPINAF	9.05	(3.53, 22.87)
		SPAF I	21.59	(9.26, 49.34)
		CAFA	21.25	(9.12, 48.48)
		BAATAF	4.43	(1.22, 15.85)
		AFASKA I	15.87	(7.30, 34.11)
Risk	Intracranial haemorrhage (fatal/non-fatal)	ARISTOTLE	8.02	(6.73, 9.56)
		RELY	7.41	(6.01, 9.12)
		ROCKET-AF	7.02	(5.67, 8.67)
		SPINAF	2.26	(0.12, 12.62)
		SPAF I	8.64	(2.37, 30.82)
		CAFA	4.25	(0.22, 23.56)
		BAATAF	2.22	(0.11, 12.32)
		AFASKA I	0.00	(0.00, 10.04)
	Extracranial haemorrhage (fatal/non-fatal)	ARISTOTLE	22.76	(20.51, 25.26)
		RELY	26.69	(23.96, 29.71)
		SPINAF ²	13.57	(6.25, 29.07)
		SPAF I ²	8.64	(2.37, 30.82)
		CAFA ²	17.00	(6.64, 42.64)
		BAATAF ²	15.52	(7.56, 31.27)
		AFASKA I ²	0.00	(0.00, 10.04)

¹ incl. unspecified stroke² Major extracranial haemorrhage

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3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. n/a

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8. Manuscript title (first six words are sufficient)

Benefit-risk assessment in a post-market setting: A case study integrating real-life experience into benefit-risk methodology

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Shahrul Mt-Isa

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The authors Steven Hobbiger, Lesley Wise and Simon Ashworth are employed in companies that markets a generic version of Warfarin, the companies general funding as "benefit in kind" was provided by GSK and Takeda as part of the PROTECT project.

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Benefit-risk assessment in a post-market setting

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Dr Simon Ashworth

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My employer, GlaxoSmithKline, markets a generic version of Warfarin.

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Benefit/Risk Assessment in a Post-Market Setting

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Stephen Franz Hobbiger

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Davide Luciani

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warfarin Benefit/Risk Assessment in a Post-Market Setting

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Alain Micaleff

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