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REGULAR ARTICLE

Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: A systematic review and meta-analysis

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Abstract

Objective: To compare the effectiveness of aspirin, warfarin, and ximelagatran as thromboprophylaxis in patients with non-valvular atrial fibrillation (NVAF).
Methods: Systematic review of randomised controlled trials in patients with NVAF treated with adjusted-dose warfarin and aspirin, fixed low-dose (FLD) warfarin, ximelagatran or placebo. Outcome measures studied were ischaemic stroke, systemic embolism, mortality and haemorrhage. Meta-analysis was performed using a fixed effects model.
Results: We identified 13 trials (n = 14,423 participants) of sufficient quality to be included in the analysis. Adjusted-dose warfarin significantly reduced the risk of ischaemic stroke or systemic embolism compared with aspirin (relative risk [RR] 0.59; 95% confidence interval [CI]: 0.40 to 0.86), FLD warfarin (RR 0.36; 95% CI: 0.23 to 0.58), or placebo (RR 0.33; 95% CI: 0.24 to 0.45). However, aspirin and placebo had a lower risk of major bleeding compared to warfarin (RR 0.58; 95% CI: 0.35 to 0.97 and RR 0.45; 95% CI: 0.25 to 0.82, respectively). The oral direct thrombin inhibitor, ximelagatran was as effective as adjusted-dose warfarin in the prevention of ischaemic strokes or systemic emboli (RR 1.04; 95% CI: 0.77 to 1.40) with less risk of major bleeding (RR 0.74; 95% CI: 0.56 to 0.96). Adjusted-dose warfarin significantly reduced mortality compared to placebo (RR 0.69; 95% CI: 0.53 to 0.89), but not for any of the other comparisons (aspirin: RR 0.87; 95% CI: 0.67 to 1.13; FLD warfarin: RR 1.11; 95% CI: 0.81 to 1.52; ximelagatran: RR 1.04; 95% CI: 0.86 to 1.26).

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Conclusions: We have extended previous analyses, making this the largest systematic review and meta-analysis of thromboprophylaxis trial data in AF — and have included recent trials with the new oral direct thrombin inhibitor, ximelagatran. This systematic review confirms the superiority of anticoagulation therapy over aspirin as thromboprophylaxis in patients with NVAF. The new oral direct thrombin inhibitor, ximelagatran, appears as effective as adjusted-dose warfarin for the prevention of thromboembolic events in NVAF, with a lower risk of bleeding.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and is associated with a 5-fold increase in the risk of stroke and thromboembolism [1]. When AF occurs in association with stroke there is a higher mortality, greater disability and lower discharge rate to own home, as well as a relatively high (15%) risk of stroke recurrence within a year, if untreated [1—3].

The available treatments for stroke prevention for AF have been studied in large randomised controlled trials that have tested adjusted-dose warfarin, fixed low-dose (FLD) warfarin and aspirin, and the results have been assessed by systematic review [4—8]. Although the results of this research have generally shown that adjusted-dose warfarin is more effective than aspirin at reducing strokes, albeit with an increase in bleeding complications [4,5,7,8], one systematic review [6] did conclude that the heterogeneity in the available trials was too great to make any definitive decision about the two treatments, although the selection criteria for this review has been criticised. These trials have also been criticised for only including a minority of subjects who were screened for inclusion, although recent studies [9—11] have suggested that trial data may well reflect clinical practice in terms of benefits in stroke reduction and risks of bleeding. Nonetheless, anticoagulation with warfarin is limited by the inconvenience of regular monitoring and the risks of bleeding, as well as a wide variation in published guidelines and management strategies (and disagreement) amongst clinicians regarding the best treatment strategies [12—14]. In addition, many patients with AF possess very limited knowledge of AF as well as its consequences and therapy [15].

Since publication of the most recent meta-analysis [8], new data have emerged in AF thromboprophylaxis for a new class of oral anticoagulant, the oral direct thrombin inhibitors. The first of the latter agents, ximelagatran, is administered orally in a fixed dose, with predictable and reproducible pharmacokinetics, low potential for drug interactions, unaffected by food or alcohol and without the need for coagulation monitoring [16]. Ximelagatran 36 mg bd has been compared with adjusted-dose warfarin in two large randomised clinical trials [17,18] but has not been directly compared with either aspirin or FLD warfarin. Given the generally accepted lower efficacy of the latter treatment regimens, it seems unlikely that direct head-to-head randomised clinical trials comparing ximelagatran with aspirin or FLD warfarin will ever take place.

When such direct comparisons are unavailable, it is possible to perform an indirect comparison, providing there is a common comparator in the available trials [19—21]. While the results of an indirect comparison should be treated with caution, a recent review of 44 meta-analyses (from 26 systematic reviews) has shown that in 41 of the 44 comparisons assessed, the indirect analysis resulted in the same conclusion from subsequent direct comparison of treatments [22].

The aim of this study was to perform a systematic review on the most recent data on thromboprophylaxis in AF using warfarin, FLD warfarin, aspirin and ximelagatran, as well as to provide an indirect comparison of aspirin and FLD warfarin against ximelagatran using adjusted-dose warfarin as a common comparator. We therefore extend previous meta-analyses, making the present study the largest systematic review and meta-analysis of thromboprophylaxis trial data in AF, with inclusion of recent trials with the new oral direct thrombin inhibitor, ximelagatran.

Methods

CENTRAL, BIOSIS, EMBASE, and MEDLINE were searched for abstracts and papers. The following search terms were included in the search strategy: warfarin (or the brand names — e.g. Coumarin® or Marevan®), aspirin (or acetylsalicylic acid or the brand names — e.g. Angettes®, Caprin® or Nu-Seals®), atrial fibrillation (or atrial flutter), and clinical trial (or clinical trial, phase III or clinical trial, phase IV or controlled clinical trial or randomized controlled trial). Searching was re-

stricted to English-language publications, and completed in February 2005.

Criteria for selection of trials for inclusion were: (i) randomised controlled trial; (ii) in patients with NVAF; (iii) treated with adjusted-dose warfarin and aspirin, FLD warfarin (or FLD warfarin plus aspirin), placebo, or ximelagatran 36 mg bd; and (iv) any additional treatment given equally in the two randomised groups. The following outcomes data were extracted for analysis: ischaemic stroke or systemic embolism; all-cause mortality; major bleeds; minor bleeds. Data were extracted by one reviewer and checked for accuracy by a second reviewer.

Quality assessment

The primary method of determining the quality of trials was an assessment of method of randomisation, and concealment of allocation of the treatments used, as this has been shown to be the aspect of randomised controlled trial design likely to introduce the most bias [23,24].

Quantitative data synthesis and analyses

An intention-to-treat approach was taken, in that all patients randomised were included in the subsequent analyses. Summary estimates were calculated as relative risks (RR), with corresponding 95% confidence intervals (95% CI), with meta-analyses using a fixed effects model using the Mantel—Haenszel method [25]. Heterogeneity was assessed using a chi-square test. Analyses were done using RevMan version 4.2.4 [26], except for creation and analysis of funnel plots which was done using StatsDirect version 2.3.8 [27].

Publication bias is potentially a serious problem in a systematic review, since clinical trials that produce significant results are more likely to be published than studies that show no difference in treatment [28—32]. The possibility of publication bias was assessed visually by creating funnel plots for the primary outcome measure of ischaemic stroke or systemic embolism. However, as this assessment is subjective, a regression of normalised effect versus precision was also calculated as a test for small study effects (using a $p < 0.1$ as an indicator of a significant result) [33].

To provide a sensitivity analyses, the following alternative analyses were performed: (i) removing the quality criteria so all trials identified as potentially relevant were included in the analysis; (ii) using a random effects model using the DerSimonian and Laird method [34] for the meta-analyses; and (iii) analysing the FLD warfarin trials and FLD warfarin plus aspirin trials separately rather than combined as in the primary analysis.

Numbers needed to treat (NNTs)

As relative risks are not always the most intuitive of numbers for clinicians to base their decisions on, the relative risks for ischaemic stroke or systemic embolism were converted to annual

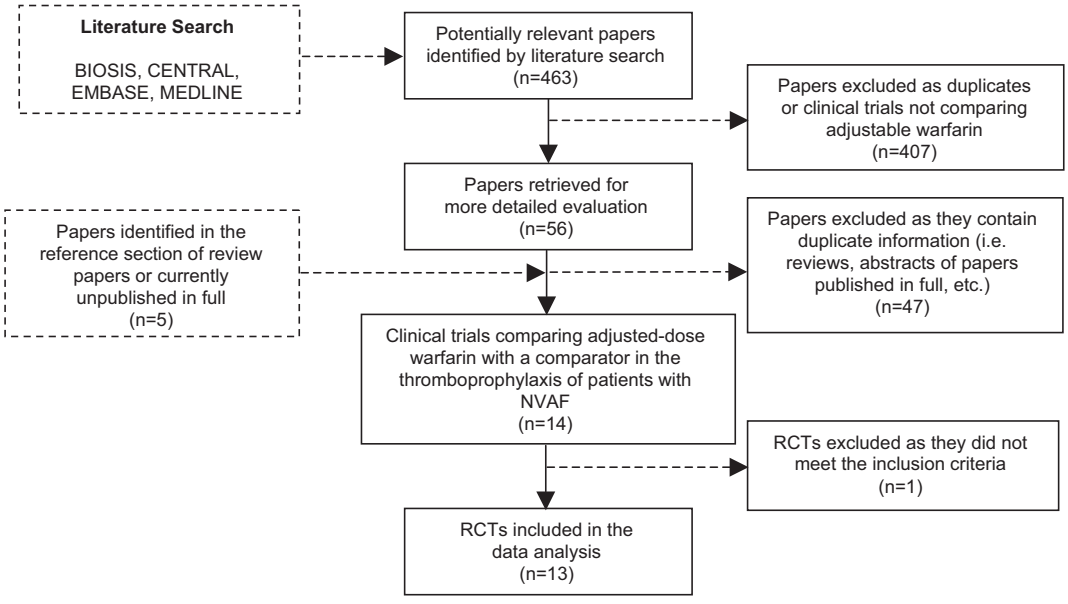

Figure 1 Results of a search of BIOSIS, CENTRAL, EMBASE, and MEDLINE, for clinical trials comparing adjusted-dose warfarin with aspirin, fixed low-dose warfarin (with or without aspirin), and ximelagatran.

Table 1 Characteristics of clinical trials considered for inclusion in the analysis

Clinical trial	Mean duration	Mean age of patients	Adjusted-dose warfarin target	Comparator(s) (daily dose)	Comment
AFASAK-I 1989 [37]	2 years	74	INR 2.8 to 4.2	Aspirin (75 mg), placebo	Mortality given as vascular deaths only
BAATAF 1990 [38]	2.3 years	68	INR 1.5 to 2.7	Placebo	Some placebo patients took aspirin
CAFA 1991 [39]	1.3 years	68	INR 2.0 to 3.0	Placebo	—
SPAF-I 1991 [40] (Group 1 Only)	1.2 years	67	Prothrombin time 1.3 to 1.8	Placebo	Only patients eligible for anticoagulation (i.e. Group 1)
SPINAF 1992 [41]	1.7 years	67	INR 1.4 to 2.8	Placebo	—
EAFT 1993 [42] (EAC Group Only)	2.3 years	71	INR 2.5 to 4.0	Placebo	Only patients eligible for anticoagulation; all strokes assumed to be ischaemic
SPAF-II 1994 [43] (Patients Aged ≤75)	2.7 years	64	Mean INR 2.7	Aspirin (325 mg)	Bleeding data from alternative paper [44]
SPAF-II 1994 [44] (Patients Aged ≤75)	2.7 years	80	Mean INR 2.6	Aspirin (325 mg)	Bleeding data from alternative paper [44]
SPAF-III 1996 [45]	1.1 years	72	INR 2.0 to 3.0	FLD warfarin plus aspirin (325 mg)	Target INR 1.2 to 1.5 with initial dose of FLD warfarin
AFASAK-II 1998 [46]	2.2 years	73	INR 2.0 to 3.0	Aspirin (300 mg), FLD warfarin, FLD warfarin plus aspirin (300 mg)	Mean INR with FLD Warf 1.14 and 1.12 with FLD warfarin plus Aspirin
MWNAF 1998 [47]	2.5 years	64	INR 2.0 to 3.0	FLD warfarin (1.25 mg)	—
PATAF 1999 [48] (EAC group only)	2.7 years	75	INR 2.5 to 3.5	Aspirin (150 mg), FLD warfarin	Only patients eligible for anticoagulation; target INR 1.1 to 1.6 with initial dose of FLD warfarin
Evans et al. 2001 [49]	2 years	78	INR 2.0 to 3.0	Aspirin (75—300 mg)	Not a randomised trial
SPORTIF-III 2003 [17]	1.5 years	70	INR 2.0 to 3.0	Ximelagatran (72 mg)	—
SPORTIF-V 2004 [18]	1.7 years	72	INR 2.0 to 3.0	Ximelagatran (72 mg)	—

EAC = eligible for anticoagulation; INR = International Normalised Ratio; FLD warfarin = fixed low-dose warfarin.

numbers needed to treat (NNTs) to provide additional clarity in the ability of the treatments examined to prevent strokes [35].

A "no treatment" baseline annual risk of stroke was taken from the US National Registry of Atrial Fibrillation stratified by $CHADS_2$ score [36]. The $CHADS_2$ score ranges from 0 to 6 and is calculated by adding 1 point for each of the following risk factors: recent congestive heart failure, hypertension, age 75 years or older, or diabetes mellitus, and adding 2 points for having had a previous stroke or transient ischaemic attack. For the sake of simplicity the scale was collapsed into high (4, 5, 6), medium (2, 3), and low risk of stroke (0, 1). NNTs were calculated by taking the "no treatment" estimate and substituting it for overall placebo event rate in the meta-analysis compared with adjusted-dose warfarin. Using these data with the relative risk from that analysis allowed calculation of an overall event rate for adjusted-dose warfarin. The overall event rate for adjusted-dose warfarin could then be filtered through the other comparisons to give standardised overall event rates.

Results

Implementation of the search strategy produced the results given in Fig. 1. Of the 14 trials identified (Table 1), 1 was not a randomised controlled trial [49] and excluded. All the remaining trials ($n = 13$ trials, with 14,423 participants) were judged to be of sufficient quality to have data extracted for inclusion in the analyses (Table 2).

Quantitative data synthesis and analyses

The meta-analysis of ischaemic stroke or systemic embolism (Fig. 2) shows a relative risk reduction in

Table 2 Data extracted from the clinical trials considered for inclusion in the analysis

Clinical trial	Comparators	*N*	Ischaemic stroke or systemic embolism	Mortality	Major bleed	Minor bleed
AFASAK-I 1989	Adj-warfarin	335	4	3	1	21
	Aspirin	336	19	12	1	6
	Placebo	336	21	15	0	0
BAATAF 1990	Adj-warfarin	212	2	11	4	38
	Placebo	208	13	26	2	21
CAFA 1991	Adj-warfarin	187	7	10	5	—
	Placebo	191	11	8	1	—
SPAF-I 1991 (Group 1 only)	Adj-warfarin	210	6	6	4	4
	Placebo	211	18	8	4	1
SPINAF 1992	Adj-warfarin	260	7	15	7	64
	Placebo	265	23	22	5	46
EAFT 1993 (EAC group only)	Adj-warfarin	225	21	41	13	47
	Placebo	214	54	44	3	11
SPAF-II 1994	Adj-warfarin	358	14	36	18	12
(Patients aged ≤75)	Aspirin	357	21	41	10	1
SPAF-II 1994	Adj-warfarin	197	14	26	16	5
(Patients aged >75)	Aspirin	188	18	24	6	1
SPAF-III 1996	Adj-warfarin	523	11	35	12	4
	FLD warfarin plus aspirin	521	44	42	13	6
AFASAK-II 1998	Adj-warfarin	170	5	17	4	42
	Aspirin	169	6	14	5	26
	FLD warfarin	167	6	6	3	21
	FLD warfarin plus aspirin	171	9	9	1	28
MWNAF 1998	Adj-warfarin	153	2	6	5	—
	FLD warfarin	150	5	7	1	—
PATAF 1999	Adj-warfarin	131	4	12	1	14
(EAC Group Only)	Aspirin	141	5	17	1	9
	FLD warfarin	122	5	8	1	8
Evans et al. 2001	Adj-warfarin	214	19	29	11	43
	Aspirin	172	33	29	2	9
SPORTIF-III 2003	Adj-warfarin	1703	48	79	41	506
	Ximelagatran	1704	36	78	29	449
SPORTIF-V 2004	Adj-warfarin	1962	38	123	84	819
	Ximelagatran	1960	47	116	63	674

EAC = eligible for anticoagulation; Adj-warfarin = adjusted-dose warfarin; FLD warfarin = fixed low-dose warfarin; — = no data reported.

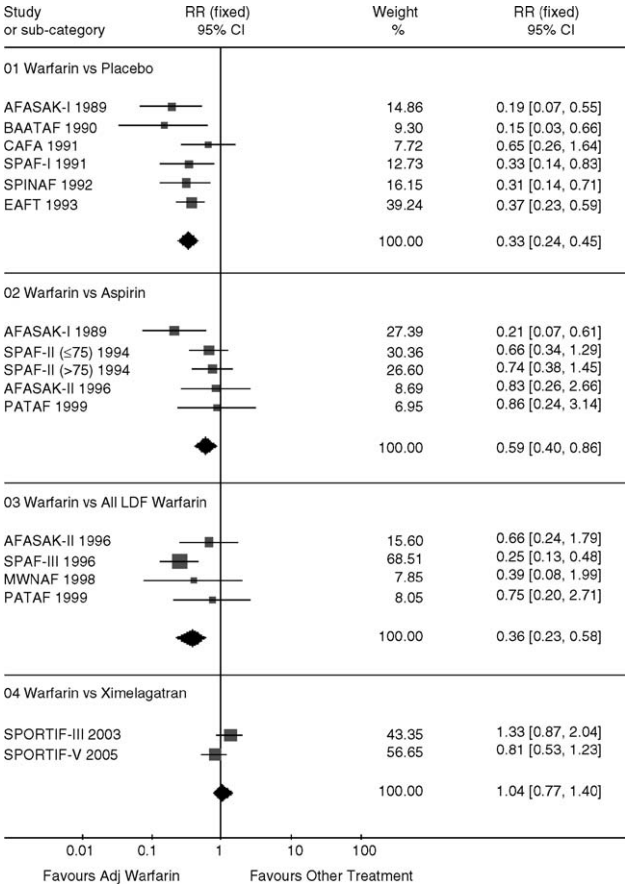

Figure 2 Meta-analysis of ischaemic stroke or systemic embolism for adjusted-dose warfarin compared with placebo, aspirin, fixed low-dose (FLD) warfarin (with or without aspirin), and ximelagatran in patients with non-valvular atrial fibrillation.

favour of adjusted-dose warfarin compared with placebo (67%, 95% CI: 55% to 76%; $p<0.00001$), aspirin (41%, 95% CI: 14% to 60%; $p=0.006$), and FLD warfarin (64%, 95% CI: 42% to 77%; $p<0.0001$). In contrast, there was a non-significant increase in relative risk of ischaemic stroke or systemic embolism with adjusted-dose warfarin compared with ximelagatran (4%, 95% CI: 23% reduction to 40% increase; $p=0.82$).

For all-cause mortality, there was a significant relative reduction in deaths with adjusted-dose warfarin compared with placebo (31%, 95% CI: 11% to 47%; $p=0.005$), but no significant difference was identified in the other comparisons (see Fig. 3).

The meta-analysis of major bleeds shows significantly fewer events with placebo (55%, 95% CI: 18% to 75%; $p=0.009$), aspirin (42%, 95% CI: 3% to 65%; $p=0.04$), and ximelagatran (26%, 95% CI: 4% to 44%; $p=0.02$) compared with adjusted-dose warfarin (Fig. 4). There was a non-significant reduction in major bleeds with FLD warfarin (24%, 95% CI: 58% reduction to 40% increase; $p=0.38$) compared with adjusted-dose warfarin.

For minor bleeds (Fig. 5), there were significantly fewer events with placebo (relative reduction 54%, 95% CI: 41% to 64%; $p<0.00001$), aspirin (55%, 95% CI: 36% to 68%; $p<0.00001$), FLD warfarin (36%, 95% CI: 11% to 54%; $p=0.007$), and ximelagatran (15%, 95% CI: 10% to 21%; $p<0.00001$), compared with adjusted-dose warfarin.

Publication bias

The limited number of trials in each of the comparisons makes assessment of publication bias difficult. Overall, there was no apparent asymmetry in the funnel plots, and no significant effects due to small trials were detected (all comparisons, $p>0.1$), suggesting that publication bias was unlikely to be an important factor (data not shown).

Assessment of heterogeneity

There was no evidence of statistically significant heterogeneity in any of the primary analyses (all $p>0.05$) except in the meta-analysis of adjusted-

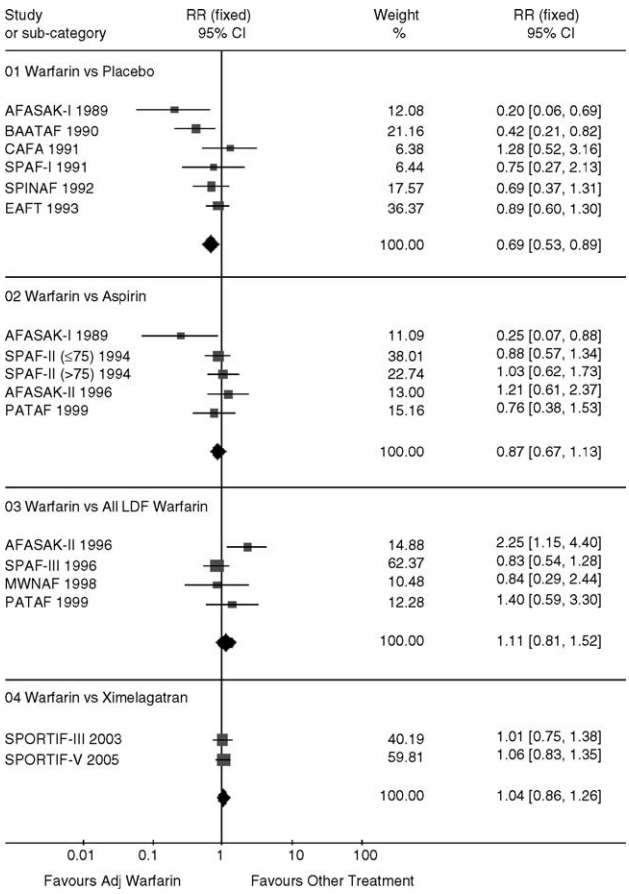

Figure 3 Meta-analysis of mortality for adjusted-dose warfarin compared with placebo, aspirin, fixed low-dose (FLD) warfarin (with or without aspirin), and ximelagatran in patients with non-valvular atrial fibrillation.

dose warfarin compared with placebo for minor bleeds ($p=0.004$). By sequentially excluding the included trials, we identified that the bulk of the heterogeneity was associated with the inclusion of the European Atrial Fibrillation Trial (EAFT) [42]. However, as all of the trials in this analysis showed a trend in the same direction, only the magnitude of the difference is in question. The heterogeneity does not affect the conclusion that would be drawn from this comparison.

Sensitivity analyses

Including the (excluded) study by Evans et al. [49] in the analysis only provides additional data for the comparison of adjusted-dose warfarin and aspirin, and made no significant difference to conclusions that would be drawn from the primary analysis. Adjusted-dose warfarin compared with aspirin had a significant relative reduction in ischaemic stroke or systemic embolism (45%, 95% CI: 26% to 60%; $p<0.001$) with a non-significant relative reduction in mortality (15%, 95% CI: 32% reduction to 7% increase; $p=0.17$). Aspirin compared with adjusted-dose warfarin had a significant relative reduction in major (49%, 95% CI: 18% to 68%; $p=0.006$) and minor bleeds (60%, 95% CI: 46% to 71%; $p<0.00001$).

The effect of using a random effects model using the DerSimonian and Laird method for the primary analyses made small numerical differences to the overall estimates but did not change the direction or make a significant difference non-significant (Table 3).

Analysing the FLD warfarin and FLD warfarin plus aspirin trials separately gives mixed results as might be expected from reducing the power in the combined analysis. FLD warfarin showed no significant difference from adjusted-dose warfarin, except with regards to minor bleeds where FLD warfarin had a significant relative reduction (47%, 95% CI: 19% to 65%; $p=0.003$). Similarly, FLD warfarin plus aspirin shows no significant difference from adjusted-dose warfarin, except with regards to ischaemic stroke or systemic embolism where adjusted-dose warfarin had a significant relative

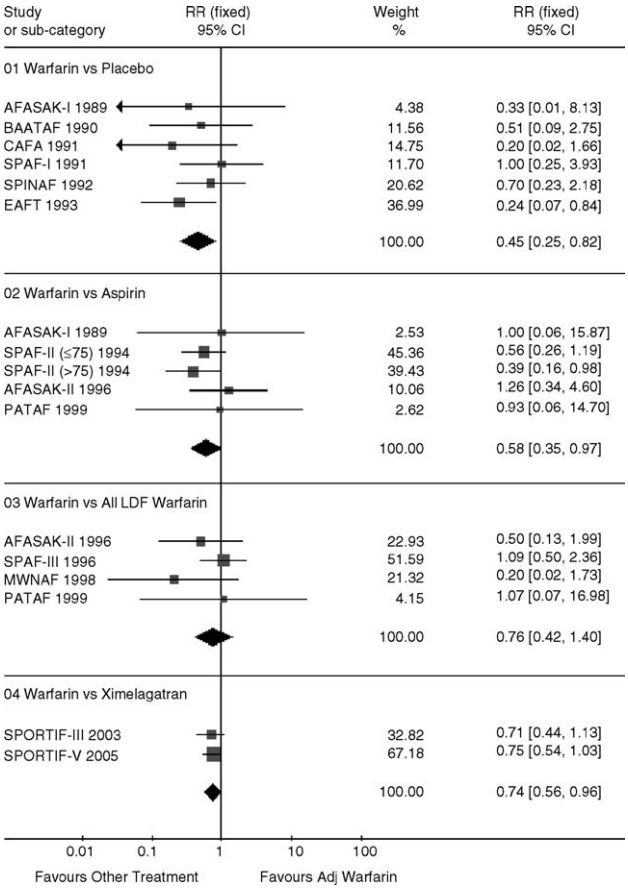

Figure 4 Meta-analysis of major bleeds for adjusted-dose warfarin compared with placebo, aspirin, fixed low-dose (FLD) warfarin (with or without aspirin), and ximelagatran in patients with non-valvular atrial fibrillation.

reduction in risk (70%, 95% CI: 48% to 83%; $p<0.0001$).

Numbers needed to treat (NNTs)

To contextualise treatment benefit in terms of stroke prevention, the relative risks calculated in the meta-analyses were converted to NNTs. The adjusted annual stroke rates, which correspond to the high, medium, and low risk of stroke with no treatment from the $CHADS_2$ classification are: 9.6%, 4.7%, and 2.6%, respectively.

The numbers of patients needed to be treated to prevent one stroke at one year for the comparators assessed are given in Fig. 6. That is, for high-risk patients, the NNT for ximelagatran and adjusted-dose warfarin is 16, while the NNTs for aspirin and FLD warfarin are 24 and 126, respectively.

Discussion

The aim of this systematic review was to compare the effectiveness of aspirin, warfarin, and ximelagatran as thromboprophylaxis in patients with NVAF. Consistent with previous systematic reviews and meta-analyses [4,5,7,8], we have confirmed the superiority of anticoagulation therapy over aspirin. Nonetheless, we have extended previous analyses by systematically reviewing data from 13 trials with 14,423 participants — making this the largest systematic review and meta-analysis of thromboprophylaxis trial data in AF — and have included recent trials with the new oral direct thrombin inhibitor, ximelagatran.

Adjusted-dose warfarin was more effective than aspirin at reducing the risk of ischaemic stroke or systemic embolism but had an increased risk of major and minor bleeds. Thus, to provide a clinically acceptable risk/benefit profile, adjusted-dose warfarin is typically used in medium-to-high-risk patients with AF while aspirin is deemed acceptable for patients at a low risk of stroke [2]. FLD warfarin was also substantially less effective than adjusted-dose warfarin at reducing the risk of ischaemic stroke or systemic embolism, with no significant difference in the risk of major bleeds, although FLD warfarin did carry less risk of minor

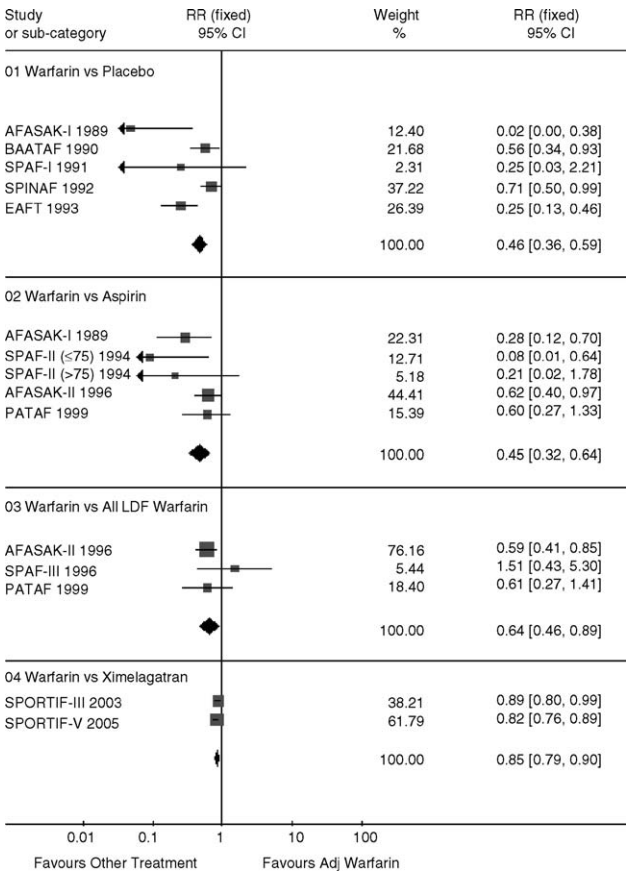

Figure 5 Meta-analysis of minor bleeds for adjusted-dose warfarin compared with placebo, aspirin, fixed low-dose (FLD) warfarin (with or without aspirin), and ximelagatran in patients with non-valvular atrial fibrillation.

bleeds; thus, an assessment of risk/benefit would not favour FLD warfarin. The lack of significant differences in mortality between any of the active treatments and adjusted-dose warfarin merits comment. One possible explanation for this could be that the majority of the events avoided are non-fatal. As non-fatal strokes carry with them significant morbidity, as well as substantial costs, treatments that reduce non-fatal strokes are still important even if they did not reduce fatal strokes. This is supported by a recent cohort study, which demonstrated that anticoagulation that results in an INR of 2.0 or greater, reduces the severity of ischaemic strokes [10]. Similarly, the risk for intracranial haemorrhage increases at age >85 years, especially with INRs of >3.5; interestingly, INRs <2.0 were not associated with lower risk for intracranial haemorrhage compared with INRs between 2.0—3.0, and therefore, anticoagulation management should focus on maintaining INRs in the 2.0 to 3.0 range, even in elderly patients with atrial fibrillation, rather than targeting INRs less than 2.0 [50].

From the comparisons of adjusted-dose warfarin and aspirin, FLD warfarin, ximelagatran or placebo, only ximelagatran was as effective as adjusted-dose warfarin in significantly reducing the risk of ischaemic stroke or systemic embolism, with a lower risk of bleeding. However, adjusted-dose warfarin is not without its disadvantages as it carries an increased risk of major and minor bleeds compared with other treatments assessed. In terms of a risk/benefit profile, this systematic review suggests that ximelagatran has the benefits of adjusted-dose warfarin with less risk of bleeding. From a clinical thromboprophylaxis point of view, an assessment of risk/benefit would favour ximelagatran over adjusted-dose warfarin.

What is not assessed in this systematic review is the cost effectiveness of the various treatment options or the development of liver enzyme abnormalities (defined as alanine transaminase levels >3 times the upper limit of normal) with the use of ximelagatran. In the clinical trials using the latter compound, this occurred in approximately 6% of patients, and was mostly asymptomatic, typically occurring 3 to 6 months after treatment initiation and returning toward baseline whether or not ximelagatran treatment was continued. These liver function changes that have been associated with

Table 3 Summary of all primary analyses comparing adjusted-dose warfarin with placebo, aspirin, fixed low-dose warfarin, and ximelagatran in patients with NVAF using a fixed effects or a random effects model (relative risk and 95% confidence intervals)

Comparator	Fixed effects	*p*-value	Random effects	*p*-value
Placebo				
— Ischaemic stroke or systemic embolism*	0.33 (0.24 to 0.45)	<0.00001	0.34 (0.25 to 0.47)	<0.00001
— All-cause mortality*	0.69 (0.53 to 0.89)	0.005	0.67 (0.44 to 1.00)	0.05
— Major bleeds†	0.45 (0.25 to 0.82)	0.009	0.48 (0.26 to 0.90)	0.02
— Minor bleeds†	0.46 (0.36 to 0.59)	<0.00001	0.39 (0.20 to 0.76)	0.005
Aspirin				
— Ischaemic stroke or systemic embolism*	0.59 (0.40 to 0.86)	0.006	0.61 (0.40 to 0.95)	0.03
— All-cause mortality*	0.87 (0.67 to 1.13)	0.29	0.88 (0.64 to 1.21)	0.42
— Major bleeds†	0.58 (0.35 to 0.97)	0.04	0.59 (0.35 to 0.99)	0.04
— Minor bleeds†	0.45 (0.32 to 0.64)	<0.00001	0.43 (0.25 to 0.74)	0.002
All FLD warfarin				
— Ischaemic stroke or systemic embolism*	0.36 (0.23 to 0.58)	<0.0001	0.41 (0.23 to 0.73)	0.003
— All-cause mortality*	1.11 (0.81 to 1.52)	0.50	1.21 (0.72 to 2.05)	0.47
— Major bleeds†	0.76 (0.42 to 1.40)	0.38	0.80 (0.43 to 1.53)	0.49
— Minor bleeds†	0.64 (0.46 to 0.89)	0.007	0.63 (0.45 to 0.87)	0.005
Ximelagatran				
— Ischaemic stroke or systemic embolism*	1.04 (0.77 to 1.40)	0.82	1.04 (0.63 to 1.70)	0.88
— All-cause mortality*	1.04 (0.86 to 1.26)	0.68	1.04 (0.86 to 1.26)	0.68
— Major bleeds†	0.74 (0.56 to 0.96)	0.02	0.74 (0.57 to 0.96)	0.02
— Minor bleeds†	0.85 (0.79 to 0.90)	<0.00001	0.85 (0.79 to 0.91)	<0.00001

* A relative risk <1.00 signifies a benefit in favour of adjusted-dose warfarin.
† A relative risk <1.00 signifies a benefit in favour of the alternative treatment.

ximelagatran treatment will need to be assessed in the "real world" setting.

While there are potential issues in calculating NNTs from the results of meta-analyses — principally that the underlying risk and the duration of the trials combined may be different which can lead to misleading NNTs [35] — our approach resolves this conflict by using a "real-life" baseline risk taken from the $CHADS_2$ classification rather than using one derived from the trials within the analysis. Calculating the NNTs based on different risks of stroke is a valid approach because the reductions in the relative risk of stroke with the available treatments are consistent across these baseline risk subpopulations [36].

The main limitation of this systematic review is that it only considers clinical trials published in the English language, as well as trials that have focused on AF thromboprophylaxis as the primary research question(s), using adjusted-dose warfarin

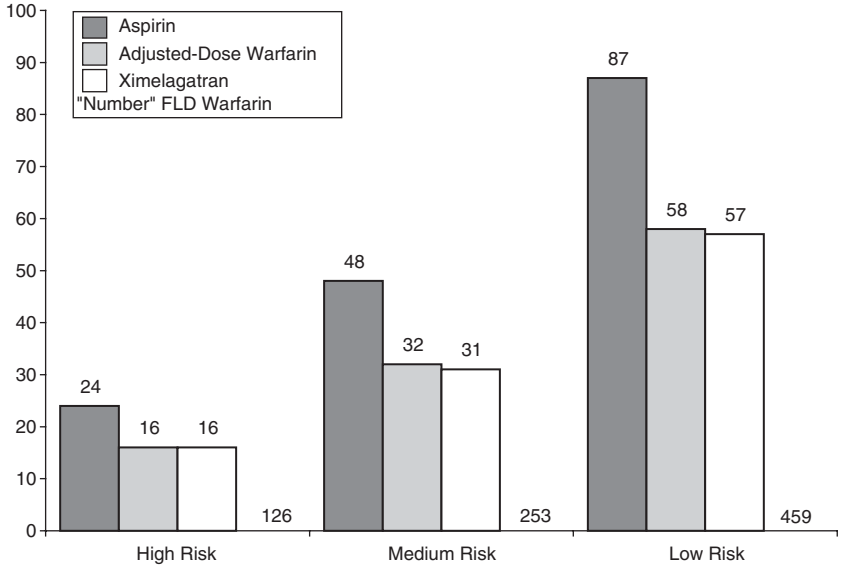

Figure 6 Number needed to treat (NNT) to prevent one stroke at one year based on underlying risk of stroke ($CHADS_2$ High/Medium/Low) in patients with non-valvular atrial fibrillation.

and aspirin, FLD warfarin, ximelagatran or placebo. In contrast to a previous meta-analysis [5], we have not included large trials of thromboprophylaxis for stroke prevention that had coincidently included (small) subgroups of AF patients [51—54]. We have also excluded trials comparing adjusted-dose warfarin strategies [55] and those investigating other experimental agents, such as indobufen, or paraenterally administered antithrombotic agents, such as heparin. Another limitation of the research is that the secondary analysis could only be calculated in a robust way for stroke as no credible "no treatment" baseline data on major or minor bleeds could be identified, which prevented the possible comparison of NNTs and NNHs (numbers needed to harm) that otherwise might have been possible. Finally, any systematic review is a snapshot of the current evidence. Large trials that are currently ongoing, such as the community-based Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial [56] or other treatment regimens compared to adjusted-dose warfarin (e.g. aspirin plus clopidogrel, factor-Xa inhibitor and pentasaccharide idraparinux, etc.) [57], could not be considered in the analysis but should be incorporated in any updated assessment once the trial results become available.

In conclusion, we have extended previous meta-analyses, and confirmed the superiority of anticoagulation therapy as thromboprophylaxis in patients with NVAF when compared to alternative treatments such as aspirin and FLD warfarin. The new oral direct thrombin inhibitor, ximelagatran, appears as effective as adjusted-dose warfarin for the prevention of thromboembolic events in NVAF, with lower risk of bleeding.

Conflict of Interest Statement

GL has received funding for research, educational symposia, consultancy and lecturing from different manufacturers of drugs used for the treatment of atrial fibrillation and thrombosis, including AstraZeneca, who manufacture ximelagatran.

SJE acted as systematic reviewer and information specialist for this study, and is currently an employee of AstraZeneca.

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