Novel Oral Anticoagulants in Atrial Fibrillation: A Meta-analysis of Large, Randomized, Controlled Trials vs Warfarin

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ABSTRACT

Background: Warfarin reduces ischemic stroke in atrial fibrillation, but has numerous limitations. Novel oral anticoagulants provide more predictable anticoagulation with fewer shortcomings.

Hypothesis: Novel oral anticoagulants are superior to warfarin to prevent stroke or systemic embolism.

Methods: Phase III randomized warfarin-controlled trials enrolling >3000 patients that reported clinical efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation were identified from MEDLINE, Embase, and Cochrane Central Register of Controlled Trials through October 2012. Two reviewers extracted data; differences were resolved by consensus. The end points analyzed were stroke or systemic embolism (primary efficacy composite); all-cause mortality, ischemic stroke, systemic embolism (individually, secondary efficacy); and hemorrhagic stroke, major bleeding (individually, safety). The Mantel-Haenszel method was used to calculate pooled relative risk (RR) and 95% confidence intervals (CI) from fixed-effects (if homogenous) or random-effects models (if heterogeneous).

Results: In 5 studies of 51895 patients, the composite of stroke or systemic embolism (RR: 0.82; 95% CI: 0.69–0.98; $P = 0.03$) and all-cause mortality (RR: 0.91; 95% CI: 0.85–0.96; $P = 0.0026$, respectively) were reduced with the novel agents. Factor Xa inhibitors significantly reduced the primary composite (RR: 0.84; 95% CI: 0.74–0.94; $P = 0.004$) and all-cause mortality (RR: 0.91; 95% CI: 0.84–0.98; $P = 0.01$). Direct thrombin inhibitor achieved results similar to the overall meta-analysis (drug class–outcome interactions $P = 0.47$ for primary outcome, $P = 1.00$ for mortality). Compared with warfarin, novel anticoagulants markedly reduced hemorrhagic stroke (RR: 0.51; 95% CI: 0.41–0.64; $P < 0.0001$).

Conclusions: Novel oral anticoagulants may be superior to warfarin in patients with atrial fibrillation, reducing the composite of stroke or systemic embolism and lowering all-cause mortality. The benefit is largely due to fewer hemorrhagic strokes.

Introduction

Atrial fibrillation increases the risk of stroke and death. Vitamin K antagonists (VKAs), such as warfarin, reduce the risk of stroke by 65%, but increase that of hemorrhage compared with placebo or aspirin.¹ Although VKAs are

recommended for patients who have atrial fibrillation and are at moderate or high risk for stroke,² these drugs have several drawbacks, including multiple interactions with food and drugs and the need for frequent laboratory monitoring. As a result, adherence is low and rates of discontinuation high.^{3,4} In addition, many patients who take VKAs still have inadequate anticoagulation.⁵ Thus, there is a need for new anticoagulant agents that are effective, safe, and more convenient to use.

Several novel oral anticoagulants have been developed in an attempt to overcome the many challenges faced by clinicians and patients with the use of VKAs.^{6–8} These novel agents share many similar theoretical advantages such as a rapid onset and offset of action, predictable pharmacokinetics that do not require ongoing monitoring of anticoagulation testing, and fewer drug-drug and food-drug interactions.⁸ Recently, several direct thrombin and factor Xa inhibitors have been investigated in

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Figure 1. Flow diagram of literature search. Abbreviations: RCTs, randomized controlled trials.

large clinical trials of patients with atrial fibrillation to establish their clinical efficacy and safety compared to warfarin, the most commonly prescribed VKA worldwide.

We aimed to compare the major clinical efficacy and safety outcomes with these new oral anticoagulants with warfarin using data from large phase III clinical trials. Our primary hypothesis was that thrombin or factor Xa inhibitors would be superior to warfarin for the prevention of the composite of stroke or systemic embolism.

Methods

Search Strategy

We searched MEDLINE, Embase, and the Cochrane Database of Systematic Reviews from August 2000 to October 2012. The search was limited to trials involving over 3000 patients with no language restriction. Key words used were atrial fibrillation, ximelagatran, melagatran, dabigatran, rivaroxaban, apixaban, stroke, and embolism. The reference lists of published meta-analyses were also reviewed. Overall, 34 articles were reviewed (Figure 1).

Eligibility of Studies

Inclusion criteria for retrieved studies were: (1) controlled comparisons of a novel oral anticoagulant vs warfarin in at least 3000 patients with atrial fibrillation, (2) randomized treatment allocation, and (3) intention-to-treat analysis.

Data Abstraction and Quality Assessment

Two independent reviewers (S.D., M.L.) performed data abstraction and used the Jadad score to assess the quality of selected articles.⁹ Consensus was used to resolve discrepancies. The end points of interest were: composite of stroke or systemic embolism (primary efficacy composite); death from any cause, ischemic stroke, or systemic embolism (secondary efficacy end points); hemorrhagic stroke, major bleeding (safety end points). One study did not present data for ischemic stroke and systemic embolism separately; therefore, the meta-analysis of this end point was carried out with the remaining studies.

Definitions of end points were the same across all trials, with the important exception of major bleeding; therefore, a formal meta-analysis was not conducted for this outcome. The Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial tested 2 different doses of dabigatran; only data concerning the highest (most effective) were used. Data were used from the intention-to-treat populations unless otherwise specified.

Sensitivity Analysis

Because 1 of the novel oral anticoagulants (ximelagatran) will not be available for clinical use due to rare but occasionally fatal hepatotoxicity, analyses were repeated eliminating data from the 2 trials that studied ximelagatran.

Statistical Analysis

Relative risk (RR) were calculated for each study outcome to allow for pooling of similar outcomes. RRs and 95% confidence intervals (CIs) were estimated for primary and secondary end points of each trial separately and for combinations of studies using fixed- and random-effects models. The χ^2 test was used to assess heterogeneity across studies. Statistically homogenous data, defined as a χ^2 test P value >0.10 , were analyzed using fixed-effects models; the Mantel-Haenszel method¹⁰ was used to calculate pooled RRs and 95% CIs for these models. Otherwise, the random effects models was used.¹¹ The P value threshold for statistical significance was set at 0.05. The inverse of the standard error of the natural logarithm of the RR against the RR was plotted to assess the presence of publication bias.

Cochrane Q heterogeneity tests were computed and considered significant at $P < 0.10$.¹² The degree of

Table 1. Metanalytic Results

	Stroke or Embolism	Death From Any Cause	Hemorrhagic Stroke	Embolism	Major Bleeding	Ischemic Stroke
Homogeneity test (P)	0.03	0.96 ^a	0.15 ^a	0.28 ^a	0.0021	0.18 ^a
RR (95% CI) FE	0.81 (0.73-0.89)	0.91 (0.85-0.96)	0.51 (0.41-0.64)	1.08 (0.67-1.72)	0.86 (0.8-0.93)	0.87 (0.75-1.06)
RR (95% CI) RE	0.82 (0.69-0.98)	0.91 (0.85-0.96)	0.49 (0.35-0.70)	1.08 (0.60-1.93)	0.84 (0.70-1.00)	0.87 (0.72-1.06)
I^2 Inconsistency (%)	62.7	0	40.1	20	76	37.6
Egger bias (P)	0.68	0.14	0.69	0.09	0.6	0.87

Abbreviations: CI, confidence interval; FE, fixed-effects model; RE, random-effects model; RR, relative risk. ^aIn the presence of statistical homogeneity defined as a χ^2 test P value more than 0.10, data were analyzed using a fixed-effects model.

Table 2. Main Study Characteristics

Study	Drug	No. of Patients	Masking	Test	Analysis (Primary Outcome)	Follow-up, mo	Daily Dose, mg
SPORTIF III ⁶	Ximelagatran	3410	Open label	Noninferiority	ITT	Mean 16	72
SPORTIF V ⁷	Ximelagatran	3922	Double blind	Noninferiority	ITT	Mean 20	74
RE-LY ^{8a}	Dabigatran	12098	Open label	Noninferiority	ITT	Median 24	300
ROCKET AF ⁹	Rivaroxaban	14264	Double blind	Noninferiority	ITT	Median 23	20
ARISTOTLE ¹⁰	Apixaban	18201	Double blind	Noninferiority	ITT	Median 22	10

Abbreviations: ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; ITT, intention to treat; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; SPORTIF, Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation. ^aRE-LY trial included 18113 patients; there were 6015 patients excluded because they belonged to the low-dose study branch.

Table 3. Baseline Characteristics of the Patients

Characteristics	SPORTIF III		SPORTIF V		RE-LY		ROCKET		ARISTOTLE	
	Xim-elagatran	War-farin	Xim-elagatran	War-farin	Dabi-gatran	War-farin	Rivar-oxaban	War-farin	Api-xaban	War-farin
Male (%)	68	70	70	69	63.2	63.2	60.3	60.3	60.5	65
Age (y)	70.3	70.1	72	71.6	71.5	71.6	73	73	70	70
Aspirin at entry (%)	20	21	18	18	38.7	40.6	36.3	36.7	31.3	30.5
Vitamin K antagonist at entry (%)	74	73	83	83			62.3	62.5		
Long-term vitamin K antagonist therapy (%)					50.2	48.6			57.1	57.2
Risk factors for stroke ≥ 3 (%)	34	34	44	44	32.6	32.1	87	86.9	30.2	30.2
Previous stroke, TIA, or both (%)	24	24	19	18	20.3	19.8				
Previous stroke, TIA, or embolism (%)							54.9	54.6	19.2	19.7
Hypertension (%)	72	72	81	81	78.9	78.9	90.3	90.8	87.3	87.6
Diabetes (%)					23.1	23.4	40.4	39.5	25	24.9
LVD or heart failure (%)	34	34	38	38	31.8	31.9	62.6	62.6	35.5	35.4

Abbreviations: ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; LVD, left ventricular dysfunction; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; SPORTIF, Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation; TIA, transient ischemic accident.

inconsistency among studies (I^2) was estimated according to the approach used by Higgins et al.¹³ To reduce the risk of random error, heterogeneity-adjusted trial sequential analysis was applied to the meta-analysis by calculating optimal information size (OIS) monitoring boundaries, and the cumulative Z-statistics after each trial.¹⁴ A control group incidence rate was assumed to determine the OIS for detecting a 20% RR reduction in primary outcomes of 3% (approximately the median rate across trials), with 62% (Table 1) of the total variation in the meta-analysis explained by variation across trials (heterogeneity: I^2). The OIS required to yield “moderate” meta-analytic evidence based on an $\alpha = 5\%$ significance level and $\beta = 20\%$ (80% power) was calculated. Similarly, the OIS for detecting a 10% RR reduction in death from any cause, assuming a control group incidence rate of 7% and $I^2 = 0\%$ (Table 1) was calculated. The heterogeneity-adjusted and unadjusted information size was calculated as described, and applied in

the trial sequential monitoring boundaries. The cumulative Z-curve of each cumulative meta-analysis (i.e., the series of Z-statistics after each consecutive trial) was calculated, and its crossing of monitoring boundaries with the fixed-effects model or random-effects model was assessed. Solid evidence for an intervention effect was indicated by a crossing of the monitoring boundaries by the cumulative Z-curve.

Statistical calculations were performed using SPSS version 20.0 (IBM SPSS, Armonk, NY) and Trial Sequential Analysis software (The Copenhagen Trial Unit, Copenhagen, Denmark).

Results

Of the 34 studies identified, 23 were substudies or subgroups, 3 did not include warfarin as a comparator, 2 publications were reports of adverse events, and 1 was the rationale and design article (Figure 1). Five studies enrolling

Figure 2. Overall analyses of the risk of stroke or systemic embolism. Studies are grouped as thrombin inhibitors vs warfarin (SPORTIF III/V and RE-LY) and factor Xa inhibitors vs warfarin (ROCKET AF and ARISTOTLE). Single-study random-effects relative risks and 95% confidence intervals are shown by squares and horizontal lines. Overall and group pooled relative risks with 95% confidence intervals are shown by diamonds. Abbreviations: ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; SPORTIF, Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation.

51895 patients with atrial fibrillation met our criteria for analysis, including 2 with ximelagatran,^{15,16} and 1 each with dabigatran,¹⁷ rivaroxaban,¹⁸ and apixaban.¹⁹

The main study characteristics are listed in Table 2. Baseline characteristics of patients are shown in Table 3. Indications for treatment were persistent or paroxysmal atrial fibrillation in the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials; persistent, paroxysmal, or permanent atrial fibrillation in the RE-LY and Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) studies; and persistent, paroxysmal, or newly diagnosed or new onset atrial fibrillation in the Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation (ROCKET AF) trial.

The primary objectives of these 5 trials were identical, namely, to demonstrate that the novel anticoagulant was noninferior to warfarin with regard to the composite of stroke and systemic embolism. The secondary objectives varied for each study, but all studies analyzed all-cause mortality as a key secondary end point.

Primary Efficacy Outcome (Table 1)

The primary efficacy outcomes are shown in Table 1. In the overall analysis (Figure 2), the rate of the composite primary end point of stroke or systemic embolism was lower with novel oral anticoagulants compared with warfarin (RR: 0.82; 95% CI: 0.69 to 0.98; $P = 0.03$; number needed to treat to prevent 1 event [NNT] = 200). It was estimated that 60000 patients were required to yield moderate evidence based on the calculation of the OIS (Figure 3). The number of participants did not reach that size, but the cumulative Z-curve crossed the monitoring boundary.

There was no heterogeneity in the relative risk of stroke or embolism by drug class (P for interaction = 0.47). The pooled data from the 3 trials with the thrombin inhibitors ximelagatran (SPORTIF III and V) and dabigatran (RE-LY), and the pooled data from factor Xa inhibitors rivaroxaban (ROCKET AF) and apixaban (ARISTOTLE) had nearly identical relative risks for the primary composite end point (RR: 0.85; 95% CI: 0.56-1.30; $P = 0.44$ and RR: 0.84; 95% CI: 0.74-0.94; $P = 0.0045$, respectively) compared to warfarin (Figure 2).

Secondary Efficacy Analyses

The secondary efficacy analyses are shown in Table 1. The risk of death from any cause was lower with novel oral anticoagulants (RR: 0.91; 95% CI: 0.85-0.96; $P = 0.0026$) compared to warfarin (Figure 4). As the number of participants reached 42208, the calculated OIS for mortality, the cumulative Z-curve crossed the monitoring boundary, and a 9% reduction in RR (NNT = 145) was observed (Figure 5). There was no evidence of a differential effect on all-cause mortality by drug class (P for interaction = 1.00). In analyses stratified by drug class, the RRs for death were identical, with a 9% reduction favoring the newer oral anticoagulants over warfarin (thrombin inhibitor, RR: 0.91; 95% CI: 0.82-1.01; $P = 0.08$; and factor Xa inhibitor, RR: 0.91; 95% CI: 0.84-0.98; $P = 0.01$) (Figure 4).

There was a statistical trend toward a reduction in ischemic stroke with the novel anticoagulants compared to warfarin (ischemic stroke, RR: 0.87; 95% CI: 0.75-1.06; $P = 0.06$) but no difference in systemic embolism (RR: 1.08; 95% CI: 0.67-1.93; $P = 0.73$). After excluding both the SPORTIF III and V trials with ximelagatran, there were no substantial changes in the results with regard to the primary end point or total mortality (RR: 0.79; 95% CI: 0.68-0.92 and RR: 0.90; 95% CI: 0.85-0.96, respectively).

Safety End Points

Table 1 shows the results pooled for all 5 trials. Compared with warfarin, the rate of hemorrhagic stroke was cut nearly in half with the novel oral anticoagulants (RR: 0.51; 95% CI: 0.41-0.64; $P < 0.0001$). There was a trend toward less major bleeding with the novel agents compared with warfarin (RR: 0.83; 95% CI: 0.69-1.002; $P = 0.055$) and in minor bleeding (RR 0.88; 95% CI: 0.80-0.97; $P = 0.016$). There was no apparent advantage with respect to major noncerebral bleeding (RR: 0.88; 95% CI: 0.73-1.08; $P = 0.49$), in contrast to a 49% reduction in hemorrhagic stroke (see above). There were no substantial changes after exclusion

Figure 3. Trial sequential analysis monitoring boundaries for moderate evidence in the current meta-analysis. The cumulative Z-statistic crossed the monitoring boundaries before reaching the optimal information size (OIS).

Figure 4. Overall analyses of the risk of death from any cause. Studies are grouped as thrombin inhibitors vs warfarin (SPORTIF III/V and RE-LY) and factor Xa inhibitors vs warfarin (ROCKET AF and ARISTOTLE). Single-study fixed-effects relative risks and 95% confidence interval estimates are shown by squares and horizontal lines. Overall and group pooled relative risks with 95% confidence intervals are shown by diamonds. Abbreviations: ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET AF, An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation; SPORTIF, Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation.

of the data from RE-LY (data not shown). There was no significant increase in risk of myocardial infarction with

thrombin inhibitors compared with warfarin (RR: 1.19; 95% CI: 0.71-2.01).

Discussion

In this meta-analysis of the 5 large phase III trials of novel oral anticoagulants compared to warfarin in patients with atrial fibrillation, statistically significant reductions in the primary outcome of stroke or systemic embolism (18%) was observed, as well as all-cause mortality (9%) and hemorrhagic stroke (49%). The striking reduction in hemorrhagic stroke (as compared to ischemic stroke and noncerebral bleeding) suggests that the major benefits of the novel oral anticoagulants compared to warfarin are related to a lower incidence of intracerebral bleeding. There was no apparent heterogeneity in the results according to drug class (i.e., the results were consistent in the analysis limited to direct thrombin inhibitors and in analyses limited to factor Xa inhibitors).

Dabigatran (150 mg twice daily) was superior in reducing ischemic stroke as well as intracerebral bleeding compared to warfarin in the RE-LY study. Both the 110-mg dose of dabigatran and apixaban 5 mg twice daily (down-titrated to 2.5 mg in selected patients) achieved lower bleeding rates than warfarin in the RE-LY and ARISTOTLE studies, respectively.

In Figure 2, heterogeneity is present between the open label studies (SPORTIF III and RE-LY) and the double-blind studies (SPORTIF V, ROCKET AF, and ARISTOTLE), suggesting a possible introduction of bias due to study design. Open-label trials may influence patient selection for a trial, management of the patient after randomization, compliance with study drugs and protocol, retention of patients in the study, collection of follow-up information, and assessment of end points.

All previous studies of alternatives to warfarin in patients with atrial fibrillation have had specific limitations. The combination of clopidogrel and aspirin was more effective than aspirin alone,²⁰ but less effective than warfarin.²¹ Subcutaneous idraparin (a parenteral factor Xa inhibitor) was more effective than warfarin but associated with a substantially higher risk of bleeding.²²

Figure 5. Trial sequential analysis monitoring boundaries for moderate evidence in the current meta-analysis. The cumulative Z-statistic crossed the monitoring boundaries before reaching the optimal information size (OIS).

Even the first of the novel oral anticoagulant included in this meta-analysis (ximelagatran) had to be withdrawn from the European market (ximelagatran was never approved by the US Food and Drug Administration) due to hepatotoxicity. Fortunately, the latest generation of novel oral anticoagulants is not associated with an increase in hepatic adverse events and appears at least as efficacious as warfarin. Given the similarity in its mechanism of action to dabigatran, and with the prespecified intent to analyze the totality of the evidence, the data from the trials with ximelagatran were included in this study's main analyses, despite the unavailability of ximelagatran for clinical use. Regardless, it was observed in sensitivity analyses that the results were unchanged if the 2 trials with ximelagatran were excluded.

Although these newer agents have some advantages over warfarin, there are new and different challenges. First, there is no laboratory test widely available to monitor the anticoagulant effects of these new drugs. Thus, there is no objective test for whether a patient is taking the drug, which impedes assessment of adherence, and no rapid way to determine if patients are experiencing sub- or supratherapeutic levels of anticoagulation. Second, the half-lives are prolonged in patients with renal insufficiency (particularly with dabigatran), and drug concentration can be increased by several concomitant therapies that either inhibit metabolism or interfere with intestinal p-glycoprotein efflux. There have been several reports in the literature of excess bleeding with dabigatran in elderly patients with renal dysfunction²³ that raise the question of whether the superior safety profile with dabigatran observed in clinical trials will be generalizable to clinical practice. In addition, an analysis of dabigatran concluded that dabigatran was associated with a higher rate of acute coronary syndrome events,²⁴ although our meta-analysis did not find a higher rate of myocardial infarction among the 3 thrombin-inhibitor trials. Finally, no proven antidote to dabigatran, rivaroxaban, or apixaban has been tested clinically. Therefore, patients on 1 of these novel agents may be at a relative disadvantage compared to patients on VKA in the case of trauma²⁵ or need for emergency surgery.

Nevertheless, concerns about bleeding need to be counterbalanced by the finding of reductions in stroke plus systemic embolism, hemorrhagic stroke, and most importantly, total mortality observed in this meta-analysis with the novel anticoagulants when compared with warfarin. In the meantime, standard laboratory and point-of-care assays permitting rapid, easy, widely available assessment of anticoagulation with thrombin inhibitors and factor Xa inhibitors are urgently needed. Similarly, ongoing work to develop antidotes^{26,27} or therapies that could reverse the anticoagulant effects²⁸ of these novel agents would be of great clinical interest.

Conclusion

This meta-analysis of 5 large trials in patients with atrial fibrillation demonstrated improved outcomes with novel anticoagulants compared to warfarin, and included lower rates of stroke or systemic embolism, all cause mortality, and a halving of the rate of hemorrhagic stroke. There was no evidence of statistical interaction between the class of novel anticoagulant (direct thrombin inhibitor vs factor Xa inhibitor) and benefit over warfarin in these 3 key end points. An adequately powered head-to-head trial comparing a direct thrombin inhibitor with a factor Xa inhibitor is warranted to better evaluate the relative risks and benefits of these 2 classes of novel anticoagulants.

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