Safety and Efficacy of New Oral Anticoagulants in Patients with Atrial Fibrillation: A Literature Review

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Abstract

Background: Traditionally Vitamin K antagonists (VKAs), such as warfarin, have been used to reduce the risks of stroke and systemic embolism in patients with atrial fibrillation (AF). However, they are associated with increased risk of haemorrhage. Thus, there is a need for new oral anticoagulant agents that are effective, safe, and convenient to use. Recent, observational and randomized controlled clinical trials, have examined the long-term use and efficacy of new oral anticoagulants. However, their results pertaining to important secondary efficacy end points as well as safety outcomes were inconclusive.

Aim: We, therefore, performed a systematic review to examine the long-term efficacy and safety of the new oral anticoagulants namely; dabigatran, rivaroxaban and apixaban in patients with AF.

Methods: In total 286 abstracts have been screened and 21 articles have been selected and considered as relevant for this epidemiological review. The primary efficacy endpoint was the incidence of stroke or systemic embolism. The primary safety endpoint was the incidence of major bleeding.

Results: We observed that dabigatran and rivaroxaban are more efficacious than warfarin for the prevention of stroke, death and systemic embolism. Also, they decrease the risk for intracranial bleeding and appear to have a favorable safety profile, making them promising alternatives to warfarin.

Conclusions: Overall, our results support the use of the new oral anticoagulants as alternatives to warfarin for long-term anticoagulation therapy in patients with AF.

Keywords: Atrial fibrillation; Warfarin; New oral anticoagualnts; dabigatran; Rivaroxaban; Apixaban; Safety and efficacy

Introduction

Atrial Fibrillation (AF) is the most common sustained cardiac rhythm disturbance characterized by rapid and irregular beating with its increased prevalence in older age [1]. AF also increases the risks of stroke and systemic embolism. Although, traditionally used Vitamin K Antagonists (VKAs), such as warfarin, reduce the risks of stroke and systemic embolism, however, they are associated with increased risk of hemorrhage [1]. Moreover, VKAs are cumbersome to use, because of their multiple interactions with food and drugs and also because of its slow onset of action and the high inter- and intra-individual variability in reaching effective plasma concentrations [2]. In addition to this, because of the narrow therapeutic window of VKAs, frequent laboratory monitoring of antithrombotic activity in individual patients is required [2]. Apart from this, patients with underline medical condition such as renal insufficiency experience inadequate anticoagulation and are at increased risk for ischemic stroke and bleeding during VKAs therapy [3]. In addition to this, AF patients with congestive cardiac failure present increased variability in metabolism of VKAs [4]. Thus, there is a need for new oral anticoagulant agents that are effective, safe, and convenient to use.

New oral anticoagulants are categorized, on the basis of their targets, as direct thrombin or factor Xa inhibitors. Although, we were aware that the combination of catheter ablation techniques with magnetically targeted nanoparticles for ablation of autonomic ganglia involved in initiating and perpetuating AF can be envisioned. We restricted our review to the use of new oral anticoagulants as alternatives to warfarin. Direct thrombin inhibitors include AZD0837 and dabigatran, and direct factor Xa inhibitors include apixaban, betrixaban, edoxaban, LY-517717, rivaroxaban, and ym-150 [5]. New oral anticoagulants act

by specifically and directly blocking the activity of thrombin (both free and clot-bound) [5]. The drug profile of new oral anticoagulants is that they have a short half-life of 12-17 h. Also, they have a predictable and consistent anti-coagulant effect, have a low potential for drug -drug interactions and have no drug - food interactions. In addition to this, they do not require routine coagulation monitoring [6].

Recent, observational and randomized controlled clinical trials, have examined the long-term use and efficacy of new oral anticoagulants [7]. Although, these trials established the much ease and primary efficacy of new oral anticoagulants with respect to the primary end point of combined stroke and systemic embolism [7]. Also, their effect in stroke prevention was consistent irrespective of patient baseline characteristics, suggesting that the efficacy results can be applied widely [6]. However, their results pertaining to important secondary efficacy end points as well as safety outcomes were inconclusive or heterogenous [7].

We, therefore, performed a systematic review to examine the long-term efficacy and safety of the new oral anticoagulants in patients with atrial fibrillation (AF). The objective of writing this review was

- To perform a literature review to identify observational studies (or data base studies) for the association between dabigatran or rivaroxaban (new oral anticoagulant) with any of the following events (ischemic stroke, intracranial haemorrhage (ICH), GI bleeding, non-GI bleeding or acute myocardial infarction) in patients with atrial fibrillation.

- To perform a comparative analysis of the efficacy and safety of dabigatran and rivaroxaban in comparison to warfarin in patients with atrial fibrillation.

Study Design

We systematically searched the published medical research for Randomized control trials (RCTs) comparing new oral anticoagulants to warfarin in patients with AF. The Cochrane Library, Embase, MEDLINE, Science Citation Index Expanded, and ProQuest's Dissertations and Theses databases were searched from inception through July 2011 without language restriction. The following were used as Medical Subject Heading terms and/or keywords: "new oral anticoagulants," "oral thrombin inhibitors," "oral factor Xa inhibitors," "dabigatran," "rivaroxaban," "apixaban," "edoxaban," "betrixaban," "ym-150," and "LY-517717." We did not restrict our search to studies conducted in patients with AF, to avoid excluding trials that reported subgroup data on patients with AF. The Embase and MEDLINE searches were limited to clinical trials, and the Embase search was further limited to studies performed in humans. The Science Citation Index Expanded and ProQuest searches were limited to full text reports. Clinical trial databases, relevant reviews, and the reference lists of retrieved reports were hand searched for potentially relevant studies not identified in our electronic database search.

The PRISMA statement for reporting systematic reviews and meta-analyses of RCTs5 was used for the method of this study.

Our electronic search identified a total of 3,167 reports (Figure 1). After removing duplicates, we screened titles and abstracts, and the full text of 44 publications was retrieved and evaluated for eligibility.
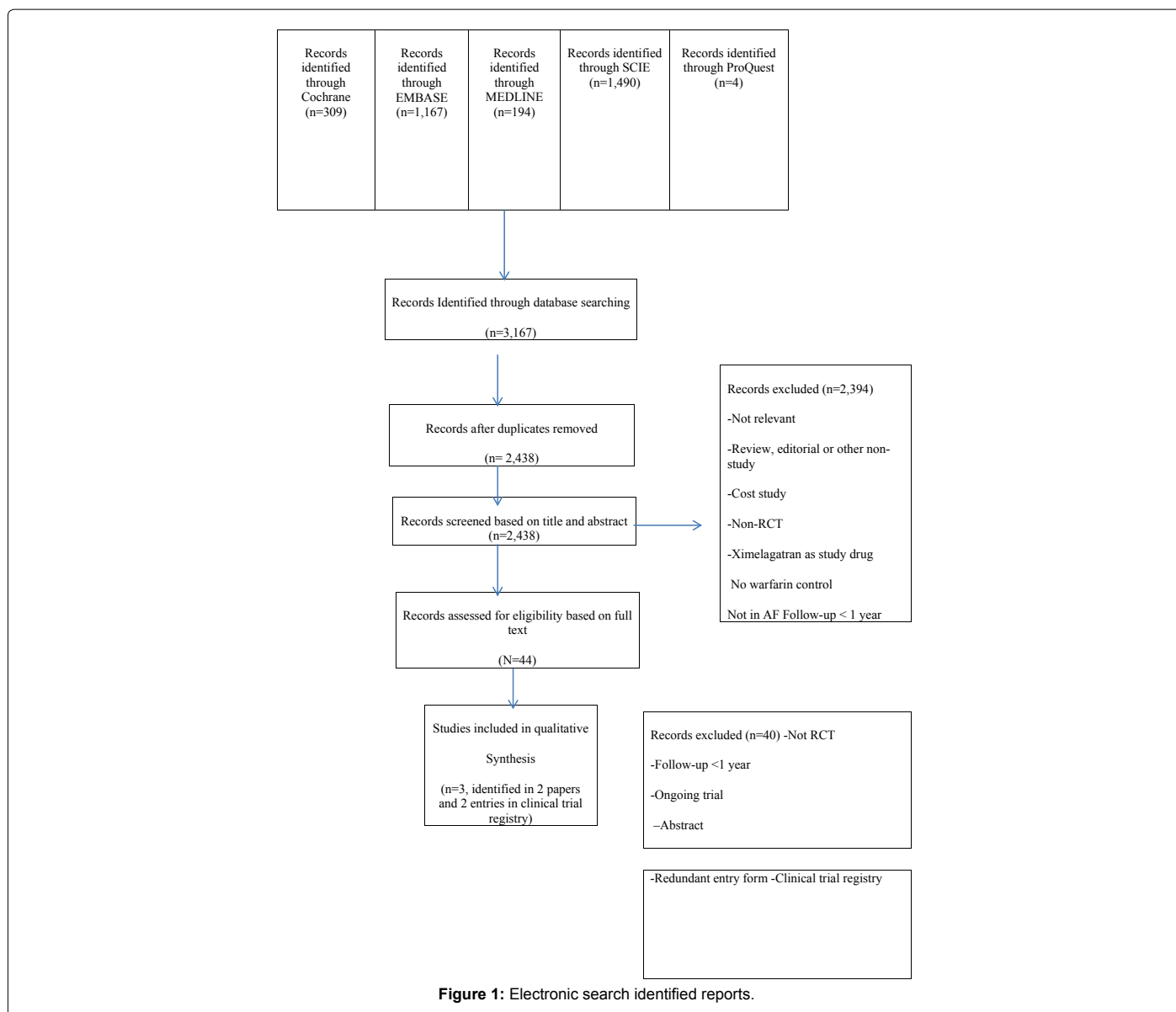

Figure 1: Electronic search identified reports.

Three trials that met our inclusion criteria were identified and included in the present study. One trial was published as an original report [8] with a follow-up report providing additional data [9]. The other 2 trials were presented as ClinicalTrials.gov entries and were subsequently published in peer-reviewed journals [10,11]. No additional studies were identified from Cochrane systematic reviews, manual searches of the reference lists of retrieved reports, relevant reviews, or clinical trial databases.

The main efficacy outcome of interest was a composite end point of stroke (including hemorrhagic stroke) and systemic embolism. Other efficacy outcomes were ischemic and unidentified stroke, hemorrhagic stroke, all-cause mortality, vascular mortality, and myocardial infarction. The main safety outcome of interest was major bleeding; taking into consideration that the definition of major bleeding complication varied among the studies. Other safety outcomes were gastrointestinal bleeding and intracranial bleeding.

Studies were included if (1) they were (RCTs), (2) they randomized subjects to warfarin, or to non–vitamin K antagonist oral anticoagulants, (3) they were conducted in patients with AF, and (4) they were published in peer reviewed journals. Studies examining ximelagatran were excluded because it has since been removed from the market because of hepatotoxicity [12]. Conference abstracts and presentations were also excluded, because their results may not be final, and such publications undergo more limited peer review. Open-label and blinded studies were included, because warfarin's need for monitoring makes blinding difficult. Finally, to assess the long-term efficacy and safety of these agents, only RCTs with follow-up durations of >1 year were included. In addition to this the exclusion criteria for our review was (1) presence of a severe heart-valve disorder, (2) stroke within 14 days or severe stroke within 6 months before screening; a condition that increased the risk of haemorrhage, (3) creatinine clearance of less than 30 ml per minute, active liver disease, and pregnancy.

We estimated pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) using Der Simonian and Laird random-effects models, which account for within- and between-study variability. The presence of between-study variability was assessed using the Qstatistic (with p 0.10 considered significant). All analyses were conducted using Stata version 11.0 (Stata Corp LP, CollegeStation, Texas).

Results

Dabigatran and warfarin were found to be significantly superior to warfarin with respect to a composite of stroke or systemic embolism, with no increased risk of major bleeding. In addition, dabigatran and warfarin significantly reduced the risk of death and haemorrhagic stroke, also a benefit signal was seen in reducing the risk of ischemic stroke and myocardial infarction. The below table shows that both Rivaroxaban and Dabigatran were associated with decreased risk of systemic embolism, stroke, haemorrhage and Ischemia (Table 1).

Impact on Myocardial infarction/Acute Coronary Syndrome (MI/ACS)

Of the all drugs, the risk for MI/ACS was lowest for rivaroxaban. The below table shows that the rate of Myocardial Infarction was lower with both dabigatran and rivaroxaban as compared to warfarin (Table 2).

Major bleeding complications

Overall, the risk of major bleeding complications was comparable between dabigatran and warfarin. Dabigatran was associated with a reduced risk for major bleeding complications. But there was still considerable heterogeneity among the studies. The below table (Table 3) shows that the rate of any major bleeding, Intracranial Bleeding was lower with Dabigatran and Rivaroxaban as compared to warfarin, whereas there was insignificant difference in the rate of Extracranial Bleeding and Major GI bleeding among the three drugs.

All-cause mortality

The use of dabigatran and rivaroxaban was associated with the reduction in all-cause mortality. The below table (Table 4) shows that the rate of Vascular death and all cause death was lower with Dabigatran and Rivaroxaban as compared to warfarin, however, this reduction in all-cause mortality was not statistically significant.

Main observations of our studies

The 3 included trials assessed the relative efficacy and safety of a new oral anticoagulant, apixaban, dabigatran, or rivaroxaban, compared to warfarin in patients with AF (Table 5). They were each designed to determine if the study drug was non-inferior to warfarin with respect to the composite end point of all stroke and systemic embolism.

In ARISTOTLE, 18,201 patients with non-valvular AF were randomized to either apixaban 5 mg twice daily or to warfarin. In RE-LY, 18,113 patients with non-valvular AF were randomized to 1 of 3 treatment arms: dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or warfarin. The 150 mg dose was used in our analysis because it is the dose administered to patients with AF. ROCKET

Events	Dabigatran*	Rivaroxaban*	Warfarin*	Dabigatran vs warfarin OR (95% CI) P	Rivaroxaban vs warfarin OR (95% CI) P	Rivaroxaban vs Dabigatran OR (95% CI) P
Systemic embolism	1.55	1.11	1.70	0.91 (0.75-1.12) <0.001	0.66 (0.53-0.82) <0.001	0.72 (0.58-0.90) 0.004
Stroke	1.45	1.01	1.58	0.92 (0.75-1.114) 0.44	0.64 (0.51-0.81) <0.001	0.70 (0.55-0.88) 0.002
Haemorrhage	0.12	0.10	0.38	0.31 (0.17-0.56) <0.001	0.26 (0.14-0.49) < 0.001	0.85 (0.39-1.83) 0.67
Ischemia	1.35	0.92	1.28	1.12 (0.89-1.41) 0.32	0.76 (0.59-0.98) 0.034	0.68 (0.53-0.87) 0.002

*rate/100 person-year. *rate/100 person-year depicts incidence rate of the event Using Person-Time. OR: Odd Ratio

Table 1: Risk of systemic embolism, stroke, haemorrhage and Ischemia in Dabigatran vs. Rivaroxaban vs. Warfarin.

Events	Dabigatran*	Rivaroxaban*	Warfarin*	Dabigatran vs warfarin OR (95% CI) P	Rivaroxaban vs warfarin OR (95% CI) P	Rivaroxaban vs Dabigatran OR (95% CI) P
Myocardial Infarction	0.73	0.74	0.94	1.15 (0.91-1.71) 0.071	1.18 (0.90-1.81) 0.052	1.02 (0.79-1.41) 0.81

OR: Odd Ratio

Table 2: Risk of Myocardial Infarction in Dabigatran vs. Rivaroxaban vs. Warfarin.

Events	Dabigatran*	Rivaroxaban*	Warfarin*	Dabigatran vs warfarin OR (95% CI) P	Rivaroxaban vs warfarin OR (95% CI) P	Rivaroxabanvs Dabigatran OR (95% CI) P
Any major bleeding	2.74	3.22	3.46	0.79 (0.68-0.92) 0.002	0.93 (0.81-1.07) 0.32	1.17 (1.01-1.36) 0.04
Intracranial Bleeding	0.21	0.30	0.72	0.29 (0.19-0.45) <0.001	0.41 (0.28-0.61) <0.001	1.42 (0.86-2.37) 0.17
Extracranial Bleeding	2.24	2.93	2.73	0.93 (0.79-1.09) 0.38	1.07 (0.92-1.25) 0.36	1.15 (0.99-1.35) 0.08
Major GI bleeding	1.13	1.54	1.03	1.10 (0.86-1.41) 0.43	1.50 (1.19-1.89) <0.001	1.36 (1.09-1.70) 0.007

OR: Odd Ratio

Table 3: Risk of bleeding in Dabigatran vs. Rivaroxaban vs. Warfarin.

Events	Dabigatran'	Rivaroxaban'	Warfarin'	Dabigatran vs warfarin OR (95% CI) P	Rivaroxaban vs warfarin OR (95% CI) P	Rivaroxabanvs Dabigatran OR (95% CI) P
Vascular Death	1.93	2.17	2.29	0.84 (0.69-1.02) 0.87	0.95 (0.78-1.15) 0.37	1.02 (0.89-1.27) 0.71
All cause death	3.20	3.45	3.71	0.86 (0.74-1.00) 0.59	0.93 (0.79-1.08) 0.56	0.97 (0.81-2.04) 0.77

OR: Odd Ratio

Table 4: Risk of death in Dabigatran vs. Rivaroxaban vs. Warfarin.

	Dabigatran 150 mg BID vs. warfarin	Rivaroxaban 20 mg daily vs. warfarin	Apixaban 5 mg BID vs. warfarin
Study Design			
Trial design	RCT Open blinded assessment	RCT DB DD	RCT DB DD
Sample size (n)	18,000+	14,000+	18,000+
Inclusion criteria	AF and selected risk factor(s) for embolization	AF and CHADS$_2$ ≥2	AF or flutter and CHADS$_2$ ≥1
Key exclusion criteria	Valvular AF Use of ASA ≥100 mg/day CrCl<30 ml/min	Valvular AF; Use of ASA >100 mg/day CrCl<30 ml/min	Valvular AF Need for ASA >165 mg/day SCr>2.5mg/dL or CrCl<25ml/min
Follow-up (mean)	2 yr	1.9 yr	1.8 yr
Outcome Definitions			
Primary Efficacy	Composite of systemic embolism and stroke (ischemic or hemorrhagic)		
Major Bleeding	ISTH: fatal/critical organ bleed; decrease ≥2g/dLHbg or transfusion of ≥2U blood		
Mortality	All causes		
Baseline Characteristics			
Age (years)	71 (mean)	73 (median)	70 (median)
Female (%)	36.4%	39.7%	35.2 %
CHADS2 (mean)	2.1	3.5	2.1
Previous embolic episode (%)	20% (stroke or TIA only)	55% (stroke,TIA, systemic embolism)	19% (stroke, TIA, systemic embolism)
TTR (%) (Standard 60-65%)	64%	55%	62%

RCT: Randomized Control Trials; DB DD: Double Blind Double Dummy; AF: Atrial Fibrillation; CHADS$_2$: The CHADS2 Score Is A Clinical Prediction Rule For Estimating The Risk of Stroke in Patients with Non-Rheumatic Atrial Fibrillation; C: Congestive Heart Failure; H: Hypertension: Blood Pressure Consistently Above 140/90 mmhg; A: Age ≥75 Years; D: Diabetes Mellitus; S$_2$: Prior Stroke or TIA or Thromboembolism, Where C. H, A, D Each Has A Point Of 01 Whereas, S$_2$ Has 02 Points. ASA: Acetyl Salicylic Acid; ISTH: International Society On Thrombosis And Haemostasis Bleeding Scale; TIA: Transient Ischemic Attack.

Table 5: Comparative analysis of three major studies.

AF compared a 20 mg/day dose of rivaroxaban to warfarin in 14,264 patients with non-valvular AF.

These 3 trials randomized a total of 44,563 patients, 22,327 to new oral anticoagulants and 22,236 to warfarin. The mean length of follow-up ranged from 657 to 730 days, and the average age ranged from 70 to 73 years. Mean CHADS2 scores were between 2.1 and 3.5. Women constituted 35% to 40% of the study populations, and the mean time in the therapeutic range of warfarin ranged from 55% to 64%.

Quality assessment of included trials was conducted using the Cochrane tool for assessing risk for bias. In RE-LY, patients were un-blinded with respect to dabigatran or warfarin assignment.

However, all investigators, coordinating centre members, the steering committee, the event adjudication committee, and the sponsor were blinded during event ascertainment and analyses. As such, the risk for bias for RE-LY was described as low for the domain of blinding.

Efficacy outcomes

In each trial, the new oral anticoagulants were found to be at least non-inferior to warfarin for the composite end point of stroke (including haemorrhagic stroke) and systemic embolism (Table 6). ARISTOTLE and RE-LY further demonstrated the superiority of apixaban and dabigatran, respectively, to warfarin with respect to this composite end point. All 3 drugs were associated with a significantly decreased risk for hemorrhagic stroke compared to warfarin. RRs of other secondary efficacy outcomes, including ischemic stroke, all-cause mortality, vascular mortality, and myocardial infarction, were also more or less comparable or inconclusive.

Safety outcomes

With regard to safety, dabigatran and rivaroxaban were found to have comparable risks for major bleeding to warfarin, while apixaban demonstrated superiority for this outcome. Gastrointestinal bleeding

Comparison of Efficacy Results						
	RE-LY		ROCKETAF		ARISTOTLE	
Outcome (%/year)	Dabigatran 150mg BID vs. warfarin	p Value	Rivaroxaban 20mg daily vs. warfarin	p Value	Apixaban 5 mg BID vs. warfarin	p Value
Primary Outcome Stroke or systemic embolism	1.1 vs. 1.7%	p<0.001 NNT 88	2.1 vs. 2.4%	p=0.12	1.3 vs. 1.6%	p=0.01 NNT 167
Stroke	1.0 vs. 1.6%	p<0.001 NNT 88	1.65 vs. 1.96%	p=0.09	1.2 vs. 1.5%	p=0.01 NNT 175
Ischemic stroke	0.9 vs. 1.3%	p=0.03 NNT 132	1.3 vs. 1.4	p=0.58	0.97 vs. 1.05%	p=0.42
Hemorrhagic stroke	0.1vs0.4%	p<0.001 NNT 182	0.26 vs. 0.44%	p=0.02 NNT 333	0.24 vs. 0.47%	p<0.001 NNT 238
All cause death	3.6 vs. 4.1%	p=0.051	4.5 vs. 4.9%	p=0.15	3.5 vs. 3.9	p=0.047 NNT 132
MI/ACS	0.7 vs. 0.5%	p=0.048 NNH 239	0.9 vs. 1.1%	p=0.12	0.5 vs. 0.6%	p=0.37

BID: twice a day, NNT: number needed to treat

Table 6: Efficacy comparison of Dabigatran vs Rivaroxaban vs apixaban vs Warfarin.

Comparison of Safety Results						
	RE-LY Dabigatran 150mg BID vs. warfarin		ROCKETAF Rivaroxaban 20mg daily vs. warfarin		ARISTOTLE Apixaban 5 mg BID vs. warfarin	
Major bleed	3.1 vs. 3.36%	p=0.31	3.6 vs. 3.4%	p=0.58	2.1 vs. 3.1%	p<0.001 NNT 67
Intracranial bleed	0.3 vs. 0.74%	p<0.001 NNT 116	0.5 vs. 0.7%	p=0.02 NNT 250	0.3 vs. 0.8%	p<0.001 NNT 128
GI bleed	1.5 vs. 1.0%	p<0.001 NNH 100	3.2 vs. 2.2%**	p=0.001 NNH 100	0.76 vs. 0.86%	0.37

NNT: number needed to treat; GI: Gastrointestinal bleeding

Table 7: Safety comparison of Dabigatran vs Rivaroxaban vs Warfarin.

data were heterogenous among the RCTs. The new oral anticoagulants were each associated with a decreased risk for intracranial bleeding compared to warfarin (Table 7).

Discussion

This study a systematic review of randomized controlled trials was performed to compare the efficacy and safety of new oral anticoagulants to those of warfarin in patients with AF. It was observed that the new oral anticoagulants are more efficacious than warfarin for the prevention of stroke and systemic embolism in patients with AF. With a decreased risk for intracranial bleeding, they appear to have a favourable safety profile, making them promising alternatives to warfarin [13].

Warfarin is largely underused because of concerns over the need for systematic monitoring and the risk for bleeding associated with its use [14,15]. Only 50 to 60% of patients with AF indicated for anticoagulation therapy are estimated to receive it [16]. There is consequently a need for new agents that can function as alternatives to warfarin for long-term anticoagulation in AF [13]. Given the recent approval of dabigatran and rivaroxaban for stroke prevention in patients with AF by the United States Food and Drug Administration, it is essential that evidence comparing the novel treatment alternatives to warfarin be available to inform clinical decisions [13].

Previous studies seeking to identify a safe and effective alternative to warfarin for patients with atrial fibrillation have all had specific limitations. The combination of clopidogrel and aspirin was more effective than aspirin alone [17] but less effective than warfarin [18]. Subcutaneous idraparinux was more effective than warfarin but was associated with a substantially higher risk of bleeding [19].

Ximelagatran, an earlier direct thrombin inhibitor, appeared to be similar to warfarin with respect to efficacy and safety but was found to be hepatotoxic [20]. In our serial measurement of liver function, we did not find evidence of hepatotoxicity with dabigatran or rivaroxaban or apixaban.

We found that the new oral anticoagulants reduced the risk for a composite end point of stroke and systemic embolism compared to warfarin. New oral anticoagulants were also found to be associated with a lower risk for key secondary efficacy outcomes, including ischemic and unidentified stroke, haemorrhagic stroke, all-cause mortality, and vascular mortality, compared to warfarin. We found no conclusive outcome with respect to major bleeding and gastrointestinal bleeding but found a substantial decrease in the risk for intracranial bleeding. Overall, our results support the use of the new oral anticoagulants as alternatives to warfarin for long-term anticoagulation therapy in patients with AF.

The trials included in this study had a number of similar conclusions that strengthen our results particularly regarding the efficacy outcomes. Dabigatran and rivaroxaban significantly reduced stroke or systemic embolism even with the higher dose of dabigatran, moreover, the main benefit was a reduction in haemorrhagic stroke. Importantly, we found small significant absolute and relative risk reductions in mortality.

As far as safety is concerned, bleeding is an important concern in anticoagulation therapy. Although warfarin has been shown to lower the risk for stroke and thromboembolism, it is associated with an increased risk for potentially life-threatening bleeding events [21,22]. Our results suggest that new oral anticoagulants lower the risk for intracranial bleeding and, although not conclusive, may decrease the

overall risk for major bleeding events in patients with AF. The risk of major bleeding was reduced with dabigatran in the RE-LY while rivaroxaban did not result in lower rates of protocol-defined major bleeding compared to warfarin in the ROCKET-AF.

Evaluation for a summarised risk for major bleeding complications among these studies has been challenging because of the marked variation in study protocol and endpoint definition. Although there was little difference in major bleeding complications when compared with control, the rates were higher for rivaroxaban [23] and apixaban [24,25] in ACS patients. Likely, several of these patients were receiving antiplatelet therapy, and probably treated with these two agents. Additional studies are required to confirm these findings and to assess the efficacy of its use at these doses [21,22].

Also, major bleeding complication rates have been noted to increase by 40 – 70% among those receiving aspirin plus clopidogrel in the RE-LY trial [26].

Majority of these ACS patients were receiving dual antiplatelet agents. Therefore, extreme caution has to be exercised when considering combining antiplatelet and antithrombotic agents because of the high bleeding risk.

Even so, the favourable net clinical benefit of dabigatran and rivaroxaban over warfarin suggested by this study (lower stroke and at least similar major bleedings), with the additional practical advantage of no requirement for INR monitoring or dose adjustment, is quite evident. On the other side, shortcomings of NOACs compared to warfarin include the short half-life, thus potentially increasing the risk of stroke or systemic embolism due to poor drug adherence, lack of coagulation assays to precisely measure the anticoagulation effect, lack of antidote for reversing anticoagulation in emergent situations, and costs. Importantly, dabigatran and rivaroxaban are not currently recommended in AF patients with other reasons for warfarin therapy, such as those with prosthetic heart valves.

Our review showed that as compared to rivaroxaban, dabigatran was associated with increased risk for acute coronary events. The excess risk associated with dabigatran was comparable to the findings of the earlier meta-analysis [27]. Therefore, it appeared that the coronary risk differed between oral direct thrombin inhibitors and anti-Xa agents. Although, the variation in the use of antiplatelet agents could have accounted for some of these differences, it was interesting to note that as compared to rivaroxaban, dabigatran was associated with a higher risk for MI/ACS in clinical studies of ACS patients [28-30]. Majority of them would have been treated with at least one antiplatelet agent. Therefore, based on these findings, those with heightened coronary risk, the use of anti-Xa agents may be preferable to direct thrombin inhibitors.

The benefit of dabigatran may be explained in part by the twice-daily dosing regimen. Since dabigatran has an elimination half-life of 12 to 17 hours, twice-daily dosing reduces variability in the anticoagulation effect, especially as compared with the anticoagulation effect of warfarin, which is difficult to control [31,32]. Warfarin broadly inhibits coagulation (inhibiting factors II, VII, IX, and X and proteins C and S). By selectively inhibiting only thrombin, dabigatran may have antithrombotic efficacy while preserving some other hemostatic mechanisms in the coagulation system and thus potentially mitigating the risk of bleeding.

Several phase II trials have demonstrated either a comparable risk or a reduced trend of major and clinically relevant bleeding

associated with the new agents compared to warfarin. Edoxaban, a new factor Xa inhibitor, was associated with similar bleeding risks as warfarin in patients with AF at once-daily dosages [21,22]. Its efficacy and safety at these dosages are being investigated in a large phase III trial [33]. A study conducted in Japanese patients with AF reported a decreased incidence of major and clinically relevant bleeding events in patients receiving apixaban compared to those receiving warfarin [34]. AZD0837, another new direct thrombin inhibitor, has also shown a trend toward lower risks for major and clinically relevant bleeding at specific doses in patients with AF [25,26]. Furthermore, there was discordance in the main findings of SPORTIF III [35] and SPORTIF V [32]. Although, both studies were similar in design, there were important dissimilarities. SPORTIF III 25 was conducted in Europe, Asia plus Australasia and SPORTIF V 26 was performed in North America. The design of the latter study [32] was double-blind but SPORTIF III was an open-label trial [36]. Of note, the primary endpoint, consisting of stroke and systemic embolism, was 2.3% per year for the warfarin group and 1.6% per year for the ximelagatran group in SPORTIF III [35]. Conversely, it was 1.2% per year for the warfarin group and 1.6% per year for the ximelagatran group in SPORTIF V [32]. There were also differences in the occurrence of major bleeding complications. The authors attributed the differences to better dose regulation, control of hypertension or hyperlipidaemia, and other differences in patient characteristics or management or chance [32]. Additional studies are required to confirm these findings and to assess the efficacy of its use at these doses. In patients after acute venous thromboembolism, dabigatran was associated with a substantially lower risk for major and clinically relevant bleeding compared to warfarin [36]. Studies of apixaban and rivaroxaban in patients after acute venous thromboembolism showed comparable risks for bleeding to low–molecular weight heparin followed by a vitamin K antagonist [37-40,35].

Our study had 3 potential limitations. First, there was heterogeneity among the included trials. They examined different oral anticoagulants, and some of the between-trial differences may be due to the use of different agents. There was also some heterogeneity with respect to the study designs and included populations. Therefore, we used random effects models that account for between-study heterogeneity. Second, patients in clinical trials are often at lower overall risk for adverse events than patients seen in every- day clinical practice. Although this may affect the generalizability of our results, it likely did not result in bias. Third, patients taking warfarin in the included studies were more likely to be within its therapeutic range than in real practice.

With >50000 patients in the present study, our analysis may have overemphasized the statistical significance of small, non-clinically relevant differences between the compared drugs. Finally, heterogeneity was present especially regarding bleeding endpoints. To account for this issue, random-effects models were privileged. Despite these limitations, a notable improvement in survival and other hard clinical outcomes was observed, with no heterogeneity issues, which is particularly interesting for patients with AF. The trials included in this review had a number of similar conclusions that strengthen our results particularly regarding the efficacy outcomes.

In patients with non-valvular AF, NOACs decrease the composite of stroke or systemic embolism, hemorrhagic stroke and mortality compared to warfarin, with no significant increase of major bleeding [6].

Based on these results, NOACs approved from regulatory agencies

should be used as first-line agents for antithrombotic management of patients with non-valvular AF.

References

1. Moe GK, Abildskov JA (1959). Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. Am Heart j 58: 59-70.

2. Mant J, Hobbs FD, Fletcher K (2007) Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA) a randomised controlled trial. Lancet 370: 493–503.

3. Singer DE, Albers GW, Dalen JE (2008) Antithrombotictherapy in atrial fibrillation: American College of ChestPhysicians Evidence-BasedClinical Practice Guidelines (8th Edition). Chest 133: 546S–592S.

4. Camm AJ, Kirchhof P, Lip GY (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 31: 2369-2429.

5. Connelly SJ, Ezekowitz MD, Yusuf S (2009) Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 361: 39-51.

6. Ansell J (2012) New oral anticoagulants should not be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation. Circulation 125: 165-170.

7. Patel M, Mahffey KW, Garg J (2011) Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med 365: 883-891.

8. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361: 1139-1151.

9. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L (2010) Newly identified events in the RE-LY trial. N Engl J Med 363: 1875-1876.

10. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, et al. (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365: 981-992.

11. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, et al. (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365: 883-891.

12. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, et al. (2009) Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 157: 805-810.

13. Diener HC (2006) Stroke prevention using the oral direct thrombin inhibitor ximelagatran in patients with non-valvular atrial fibrillation: pooled analysis from the SPORTIF III and V studies. Cerebrovasc Dis 21: 279-293.

14. Connelly SJ, Ezekowitz MD, Yusuf S (2009) Dabigatran versus Warfarin in Patientswith Atrial Fibrillation. N Engl J Med 361:1139-1151.

15. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, et al, (2008) Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 133: 160S-198S.

16. Wysowski DK, Nourjah P, Swartz L (2007) Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. Arch Intern Med 167: 1414-1419.

17. The Active Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, et al. (2009) Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 360: 2066-2078.

18. ACTIVE Writing Group of the ACTIVE Investigators (2006) Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 367: 1903-1912.

19. Amadeus Investigators, Bousser MG, Bouthier J (2008) Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. Lancet 371: 315-321.

20. Deiner HC, Executive Steering Committee of the SPORTIFF III and V Investigators (2006) Stroke prevention using the oral direct thrombin inhibitor ximelagatran inpatients with non-valvular atrial fibrillation: pooled analysis from the SPORTIF III and V studies. Cerebrovasc Dis 21: 279-293.

21. Weitz JI, Connolly SJ, Patel L, Salazar D, Rohatagi S, et al. (2010) Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost 104: 633-641.

22. Chung N, Jeon HK, Lien LM, Lai WT, Tse HF, et al. (2011) Safety of edoxaban, an oral factor Xainhibitor, in Asian patients with non-valvular atrial fibrillation. Thromb Haemost 105: 535-545.

23. Mega JL, Braunwald E, Wiviott SD, (2012) Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 366: 9-19.

24. APPRAISE Steering Committee and Investigators (2009) Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) Trial. Circulation 119: 2877-2885.

25. Alexander JH, Lopes RD, James S, (2011) Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 365: 699-708.

26. Eikelboom JW, Wallentin L, Connolly SJ, (2011) Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation. An analysis of the Randomized Evaulation of Long-Term Anticoagulation Therapy (RE-LY) Trial. Circulation 123: 2363-2372.

27. Uchino K, Hernandez AV (2012) Dabigatran association with higher risk of acute coronary events. Meta-analysis of nononferiority randomized controlled trials. Arch Intern Med 172: 372-402.

28. Oldgren J, Budaj A, Granger CB (2011) Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J 32: 2781-2789.

29. Ezekowitz MD, Reilly PA, Nehmiz G (2007) Dabigatran with and without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 100: 1419-1426.

30. Eriksson BI, Dahl OE, Huo MH (2011) Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II). Thromb Haemost 105:721-729.

31. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF (2006) Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 37: 1070-1074.

32. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S (2007) Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 115: 2689-2696.

33. Connolly SJ, Pogue J, Eikelboom J (2008) Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 118: 2029-2037.

34. Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, et al. (2010) Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: Design and rationale for the Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction Study 48 (ENGAGE AF-TIMI 48). Am Heart J 160: 635-641.

35. EINSTEIN Investigators (2010) Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 363: 2499-2510.

36. Ogawa S, Shinohara Y, Kanmuri K (2011) Safety and efficacy of the oraldirect factor Xainhibitorapixaban in Japanese patients with non valvular atrial fibrillation. The ARISTOTLE J study. Circ J 75: 1852-1859.

37. Lip GYH, Rasmussen LH, Olsson SB, Jensen EC, Persson AL (2009) Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized dose-guiding, safety, and tolerability study of four doses of AZD0837 vs. vitamin K antagonists. Eur Heart J 30: 2897-2907.

38. Olsson SB, Rasmussen LH, Tveit A, Jensen E, Wessman P, et al. (2010)

Safety and tolerability of an immediate-release for mulation of the oral direct thrombininhibitor AZD0837 in the prevention of stroke and systemic embolism in patients with atrial fibrillation. J Thromb Haemost. 103: 604-612.

39. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, et al. (2009) Dabigatran versus Warfarin in the Treatment of Acute Venous Thrombo embolism.N Engl J Med 361: 2342-2352.

40. Buller H, Deitchman D, Prins M, Segers A, Botticelli I (2008) Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. J Thromb Haemost 6: 1313-1318.