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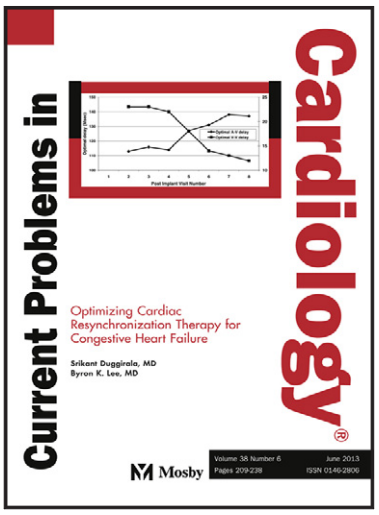

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Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation

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Gregory YH Lip: Consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi Aventis, Biotronik, BMS/Pfizer, Daiichi-Sankyo, Medtronic and BoehringherIngelheim. Speakers bureau for Bayer, BMS/Pfizer, BoehringherIngelheim, Daiichi-Sankyo, Medtronic and Sanofi Aventis.

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Biographical sketch (less than 100 words)

KeitaroSenoo

Dr Senoo has a broad background in arrhythmia, with specific training and expertise in key research areas for atrial fibrillation (AF). As an electrophysiology fellow at the The Sakakibara Heart Institute of Okayama in Japan, Dr Senoo first developed his interest into AF and its management. At the Cardiovascular Institute in Japan, he expanded his research to include epidemiological studies associated with AF, leading to several peer-reviewed publications.

Deirdre A Lane

Dr Lane is a Senior Lecturer in Cardiovascular Health at the University of Birmingham and is based in a busy inner-city teaching hospital. The main focus of her recent work has been atrial fibrillation (AF), with two major research themes: bleeding and stroke risk stratification and patient-centred research. She is a co-author of both the CHA_2DS_2-VASc stroke risk stratification score and the HAS-BLED bleeding risk score. Her other main research interest is how AF affects quality of life and psychological well-being, patient education, and patients' perceptions of AF.

Gregory YH Lip

Professor Lip is Professor of Cardiovascular Medicine at the University of Birmingham and is based in a busy city centre teaching hospital. Professor Lip has had a major interest into the epidemiology of AF, as well as the pathophysiology of thromboembolism in this arrhythmia. Furthermore, he has been researching stroke and bleeding risk factors, and improvements in clinical risk stratification. The CHA_2DS_2-VASc and HAS-BLED scores - for assessing stroke and bleeding risk, respectively – were first proposed and independently validated following his research, and are now incorporated into international guidelines.

Abstract

The availability of four non-Vitamin K oral anticoagulants (NOACs), that is, dabigatran, rivaroxaban, apixaban and edoxaban, have changed the landscape of stroke prevention in patients with atrial fibrillation. This review article provides an overview of the four phase III studies that have compared these NOACs, examining major outcomes of efficacy and safety. A range of practical questions relating to the NOACs have emerged, including topics such as patient selection, treating patients with renal impairment, treating elderly patients, and combining anticoagulant therapy with antiplatelet drugs. We also address the interaction of various patient characteristics with the treatments and suggest the features can assist the physician in the choice of a particular NOAC for particular patient(s).

KEYWORDS Non-valvular atrial fibrillation; oral anticoagulants; stroke prevention

Abbreviations

AF = Atrial fibrillation; VKAs = vitamin K antagonists; NOACs = novel oral anticoagulants; $CHADS_2$ score = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and previous stroke/transient ischemic attack; OD = once daily; BID = twice daily; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack; ITT = intention-to-treat

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia and a major cause of morbidity and mortality in clinical practice. AF increases the risk of stroke 5-fold and is responsible for at least 20% of all strokes.[1, 2] Until recently, the use of oral anticoagulation with the vitamin K antagonists (VKAs) provided the most effective standard therapy to prevent stroke and systemic embolism in patients with AF, since it reduces the risk of stroke by 64% and all-cause mortality by 26%, compared to placebo/control.[3, 4]

However, the VKAs have important limitations.[5,6] The variable anticoagulant response, food and drug interactions, and the narrow therapeutic window require close laboratory monitoring and frequent dose adjustments.[7] Poor compliance and/or inadequate anticoagulation control (as reflected by average time in therapeutic range, TTR) can lead to increased adverse events whilst on VKA therapy.[8] Indeed, the TTR can be influenced by many clinical factors, including various comorbidities associated with AF per se.[9] This complicates the management of patients with AF, leading to underuse of VKAs despite the focus of older guidelines on identifying 'high risk' patients who should be targeted for VKA therapy.[10]

In the last decade, several non-VKA oral anticoagulants (NOACs) have emerged as potential alternatives to VKAs for the prevention of ischemic stroke and systemic embolism in patients with AF. NOACs previously referred to 'novel' or 'new' oral anticoagulants, but more recently, the terminology became more confusing with Europeans referring to 'direct oral anticoagulants (DOACs)' and North Americans referring to 'target specific oral ancoagulants (TSOCs) in

publications and meeting lectures. We have proposed the retention of the acronym NOAC to refer to 'non-VKA oral anticoagulants', thereby allowing consistency with older papers.[11]

The four NOACs, which include the oral direct thrombin inhibitor, dabigatran, and the oral Factor Xa inhibitors, rivaroxaban, apixaban and edoxaban, have predictable pharmacokinetics, with a stable, dose-related anticoagulant effect and few drug interactions, hence allowing for fixed dosing without the need for regular monitoring of anticoagulation status.[12] Therefore, the management of patients on any of the new agents is distinctly different from that of individuals on warfarin.[13,14,15]

This review article provides an overview of the four phase III studies (ROCKET AF[16], ARISTOTLE[17], ENGAGE AF-TIMI 48[18], and RE-LY[19]) that compared these NOACs, examining major outcomes of efficacy and safety. A range of practical questions relating to the NOACs have emerged, including topics such as patient selection, treating patients with renal impairment, treating elderly patients, and combining anticoagulant therapy with antiplatelet drugs. We also address the interaction of various patient characteristics with the treatments and suggest the features can assist the physician in the choice of NOAC for particular patient(s).

Trial designs

One trial, the RE-LY trial was conducted as open trial, based on a prospective randomised, open blinded endpoint (PROBE) design. The other trials (ROCKET-AF, ARISTOTLE, ENGAGE-AF) were all conducted as double blind, double dummy trials with sham INRs, which requires elaborate

procedures to maintain blinding. In a recent analysis, O'Neil et al[20] reviewed the odds ratios of results across PROBE and double blind studies and outcomes, and found that amongst VKA-control subjects, event rates for stroke or systemic embolism in PROBE trials at 1.74 %/year (95% confidence interval: 1.54-1.95) was not significantly different from that in double-blind trials, at 1.88 (1.73-2.03). Among other outcomes, O'Neil et al[20] also observed VKA-treated subjects in both trial designs had similar event rates, apart from higher all-cause mortality in ROCKET-AF, and lower myocardial infarction rates in PROBE study patients.

Similarities and differences between the NOACs

There are important differences in clinical pharmacology among the four NOACs, with significant implications for their clinical use (**Table 1**). Rivaroxaban, apixaban, and edoxaban are direct factor Xa inhibitors. Dabigatran reversibly inhibits the active site of thrombin (IIa). Dabigatran etexilate is a pro-drug that is rapidly converted into the active compound dabigatran by esterases. Dabigatran possesses a lower bioavailability (6.5%) than other NOACs.

The plasma half-lives are similar for the four drugs ranging from 8 to 14 h. All four NOACs are substrates of the P-glycoprotein (P-gp) transporter. Dabigatran is excreted unmetabolized by the kidney (80%). One-third of rivaroxaban is cleared unmetabolized via the kidney, and the remaining two-thirds aremetabolized by the liver via CYP3A4. One-fourth of apixaban and half of edoxaban are excreted by the kidney. The recommended dosage for apixaban and dabigatran is twice daily, and for rivaroxaban and edoxaban, it is once daily.

In general, caution is needed in patients with significant renal impairment, patients concomitantly using potent P-gp or CYP3A4 inhibitors or inducers, patients ≥80years of age, and patients with low body weight. Dose adjustments for the four NOACs are also shown in Table 1. The rates of lower dose use were reported as 21% in ROCKET-AF, 4.7% in ARISTOTLE and 25.3% in ENGAGE AF-TIMI 48. In the RE-LY study, dabigatran 110mg bid and 150mg bid were separate intervention arms of the trial, in an adequately powered comparison of both doses to warfarin.

The definitions of major bleeding in the four phase III trials are shown in **Table 2**. The primary safety endpoint for all trials, except ROCKET-AF, was major bleeding defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria, whereas in ROCKET-AF, the primary safety endpoint was the composite of "major and non-major clinically relevant bleeding". In ARISTOTLE, a 2g drop in haemoglobin over 24 hours was needed to fulfil one criterion for 'major bleeding' whilst other trials did not have such a time window.

In contrast to the ARISTOTLE, ENGAGE AF-TIMI 48, and RE-LY studies, patients in the ROCKET-AF study were at higher risk of stroke (mean $CHADS_2$ score=3.5), were older, and had a previous stroke or systemic embolism in >50% of cases. The stroke risk of the RE-LY and ARISTOTLE trials were broadly similar (mean $CHADS_2$ score 2.1) whilst the stroke risk in ENGAGE-AF was intermediate (mean $CHADS_2$ score 2.8) between RE-LY/ARISTOTLE and ROCKET-AF. **Table 3** summarizes the efficacy and safety of the four NOACs compared with warfarin. The updated results are given for RE-LY.[21]

RE-LY

RE-LY[19] was a randomized, open-label, phase III trial of stroke or systemic embolism prevention in patients with nonvalvular AF. A total of 18,113 patients were blindly randomized to 2 doses of dabigatran, 110 or 150 mg bid, or to dose-adjusted warfarin (INR 2.0–3.0). Patients had AF and ≥1 of the following criteria: previous stroke or TIA; symptomatic heart failure or LVEF < 40%; ages ≥ 75 years or 65–74 years with an additional factors of diabetes mellitus, hypertension, or coronary artery disease.

Dabigatran at a dose of 150 mg bid showed superior primary efficacy outcome than warfarin (1.11% vs. 1.71% per year, *P*< 0.001 for superiority) and was associated with a similar rate of major bleeding (3.32% vs. 3.57% per year, *P* = 0.31). Both ischemic and hemorrhagic stroke occurred less frequently in the dabigatran group, at a dose of 150 mg (dabigatran 150 mg vs. warfarin 0.92% vs. 1.21% per year, *P* = 0.03; 0.10% vs. 0.38% per year, *P*< 0.001).

Dabigatran 110 mg bid was non-inferior to warfarin in the primary efficacy outcome of stroke or systemic embolism (1.54% vs. 1.71% per year, *P*< 0.001 for non-inferiority, *P* = 0.30 for superiority) and was superior with respect to the primary safety outcome of major bleeding (2.87% vs. 3.57% per year, *P* = 0.003). Ischemic stroke was similar between the dabigatran 110 mg dose group and warfarin (1.34% vs. 1.21% per year, *P* = 0.35), and hemorrhagic stroke occurred less frequently in the dabigatran 110 mg group (0.12% vs. 0.38% per year, *P* < 0.001). Intracranial bleeding occurred less frequently in the dabigatran groups (dabigatran 150 mg bid and 110 mg bid vs. warfarin: 0.30% per year and 0.23% per year vs. 0.76% per year,

respectively). Major gastrointestinal (GI) bleeding was more common in the dabigatran 150 mg bid group (dabigatran 150 mg bid vs. warfarin 1.56% per year vs. 1.08% per year).

In summary, dabigatran at a dose of 150 mg bid in the RE-LY study was associated with a lower incidence of stroke and thromboembolism but was similar in the incidence of major bleeding compared with warfarin, whereas dabigatran at a dose of 110 mg bid was associated with a similar rate of stroke and embolic occurrence and a reduced incidence of major bleeding.

ROCKET-AF

ROCKET-AF[16] was a randomized, double-blind, double-dummy, phase III trial of stroke orsystemic embolism prevention in patients with nonvalvular AF. A total of 14,264 patients were randomized to receive either rivaroxaban 20 mg once daily (od) (15 mg od if creatinine clearance was 30–49 mL/min) or dose-adjusted warfarin (INR 2.0–3.0). Inclusion criteria in the study were documented non-valvular AF occurring within six months prior to randomization and a history of previous stroke, transient ischemic attack (TIA) or systemicembolism, or ≥2 additional risk factors for stroke:heart failure or left ventricular ejection fraction (LVEF) ≤35%, hypertension, age≥ 75 years, and diabetes mellitus.

Rivaroxaban was non-inferior to warfarin in the primary endpoint of stroke or systemic embolism with an annual rate of 2.12% vs. 2.42%, respectively (P<0.001 for non-inferiority; P = 0.12 for superiority) by the intention-to-treat analysis. The rate of ischemic stroke was similar between the rivaroxaban and warfarin groups (1.34% vs. 1.42% per year, P=0.581), and

hemorrhagic stroke occurred less frequently in the rivaroxaban group (0.26% vs. 0.44% per year, *P*=0.024). The principal safety end-point, a composite of major and non-major clinically relevant bleeding events was also similar between the rivaroxaban and warfarin groups (14.9% vs. 14.5% per year, *P*=0.44), as was any major bleeding event (3.6% vs. 3.45% per year, *P*=0.576). Intracranial hemorrhage occurred less frequently with rivaroxaban than with warfarin (0.49% vs 0.74% per year; *P*=0.019). In general, ROCKET-AF showed that rivaroxaban was non-inferior towarfarin in the prevention of stroke or systemic embolism,with no difference in the risk of major and non-major clinically relevant bleeding.

ARISTOTLE

ARISTOTLE[17]was a randomized double-blind, double-dummy, phase III trial of stroke or systemic embolism prevention in patients with non-valvular AF.A total of 18,201 patients were randomized to either apixaban at a dose of 5 mg twice daily (bid) (dose reduced to 2.5 mg bid with ≥ 2 of the following criteria: age ≥80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL), or to dose-adjusted warfarin (INR 2.0–3.0). Patients had non-valvular AF and ≥1 risk factors for stroke: previous stroke, TIA, or systemic embolism; age ≥ 75 years; heart failure or left ventricular ejection fraction (LVEF <40%); diabetes mellitus; or hypertension.

Apixaban was superior to warfarin in the primary outcome of stroke or systemic embolism, with an annual event rate of 1.27% vs. 1.60% (*P*<0.001 for non-inferiority; *P* = 0.01 for superiority). This impressive 21% reduction in the primary endpoint was largely driven by a reduction in hemorrhagic stroke (0.24% vs. 0.47% per year, *P*<0.001), with no significant difference in the

ischemic stroke rate between apixaban and warfarin (0.97% vs. 1.05% per year, *P*=0.42). Major bleeding events were lower in the apixaban (2.13% vs. 3.09% per year, *P*<0.001), particularly intracranial hemorrhages (0.33% vs. 0.80% per year, *P*<0.001). Apixaban was also associated with a lower total mortality rate (3.52% vs. 3.94% per year, *P* = 0.047). The benefit of apixaban in the primary efficacy and safety outcomes was consistent across all age groups. Thus, the ARISTOTLE study showed that apixaban was superior to warfarin in the prevention of stroke or systemic embolism, and it resulted in less bleeding and lower mortality.

ENGAGE AF-TIMI 48

ENGAGE AF-TIMI 48[18] was a randomized, double-blind, double-dummy, phase III trial of stroke or systemic embolism prevention in patients with non-valvular AF. A total of 21,105 patients were blindly randomized to 2 doses of edoxaban, 60 or 30 mg od, or to dose-adjusted warfarin (INR 2.0-3.0). For patients in either edoxaban group, the dose was halved if any of the following characteristics were present at the time of randomization or during the study: estimated creatinine clearance rate of 30–50 ml/min, a body weight < 60 kg, or the concomitant use of verapamil or quinidine (potent P-gp inhibitors). Patients had non-valvular AF and ≥ 2 risk factors for stroke: previous stroke or TIA, congestive heart failure, hypertension, diabetes mellitus or age ≥75 years.

High-dose (60mg od) edoxaban was non-inferior to warfarin in the primary efficacy outcome of stroke or systemic embolism (1.18% vs. 1.50% per year, *P*<0.001 for non-inferiority) and was superior with respect to the primary safety outcome of major bleeding (2.75% vs. 3.43% per

year, *P*<0.001), particularly intracranial hemorrhages (0.39% vs. 0.85% per year, *P*<0.001). Ischemic stroke was similar between the edoxaban and warfarin (1.25% vs. 1.25% per year, *P*=0.97), and hemorrhagic stroke occurred less frequently in the edoxaban group (0.26% vs.0.47% per year, *P*<0.001). Low-dose (30mg od) edoxaban was also non-inferior to warfarin for the primary efficacy outcome (1.61% vs. 1.50% per year, *P*=0.005 for non-inferiority) and was superior with respect to the primary safety outcome of major bleeding (1.61% vs. 3.43% per year, *P*<0.001), particularly intracranial hemorrhage (0.26% vs. 0.85% per year, *P*<0.001). Ischemic stroke was more common in the edoxaban group (1.77% vs. 1.42% per year, *P*<0.001). By contrast, hemorrhagic stroke occurred less frequently with edoxaban (0.16% vs. 0.47% per year, *P*<0.001). Treatment with edoxaban was associated with lower rates of death from cardiovascular causes than warfarin: 3.17% with warfarin compared with 2.74% with high-dose edoxaban (*P*=0.01) and 2.71% with low-dose edoxaban (*P*=0.008), with similar findings for the rate of death from any cause. The annualized rate of the primary net clinical outcome (death from any cause, stroke, systemic embolic event, or major bleeding) was significantly lower with both edoxaban regimens than with warfarin: 8.11% with warfarin compared with 7.26% with high-dose edoxaban (*P*=0.003) and 6.79% with low-dose edoxaban (*P*<0.001). In summary, both once-daily doses of edoxaban in the ENGAGE AF-TIMI 48 study were non-inferior to warfarin for the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

Comparing the trials, and the different NOACs

A comparison of the main characteristics of the four trials is presented in Table 3. The studies differed in a number of important respects. ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 were blinded in both arms, but in RE-LY, warfarin therapy was open-label. In ROCKET-AF, the mean $CHADS_2$ score was higher than those in the other three studies, leading to a higher primary end-point event rate (2.4% per year in ROCKET AF vs. 1.6% in ARISTOTLE vs. 1.8% in ENGAGE AF-TIMI 48 and 1.71% in RE-LY per year, respectively).

In addition, data analyses were not identical. In the ARISTOTLE, ENGAGE AF-TIMI 48 and RE-LY trials, primary analyses were performed in the intention-to-treat (ITT) population. In ROCKET-AF, this was done as a per-protocol analysis and safety was as on-treatment analysis. All four drugs were confirmed to be non-inferior compared to warfarin. There was a general trend in favour of study drugs, but the level of significance for superiority was reached only for apixaban and dabigatran 150 mg bid but not for rivaroxaban and edoxaban in the ITT analysis. Apart for dabigatran 150 mg bid, no study drug showed significantly better ischemic stroke prevention than warfarin, with edoxaban 30mg even resulting in significantly more ischaemic strokes compared to warfarin.

On the safety side, all four new drugs significantly reduced the incidence of hemorrhagic stroke and intracranial hemorrhage. This represents a clear advantage of all four new drugs over warfarin. Interestingly, the RE-LY study initially raised a concern about a numerical increase in the rate of myocardial infarction with dabigatran 150mg bid compared with warfarin (0.74%, 0.53%; *P*=0.048). A more detailed analysis, including silent myocardial infarctions based on the

new appearance of pathological electrocardiographic Q-waves, did not show significant differences between dabigatran and warfarin. The ARISTOTLE, ENGAGE AF-TIMI 48,and ROCKET-AF studies did not corroborate an increase in myocardial infarctions with these drugs. Although all-cause mortality was significantly reduced with apixaban and edoxaban 30mg, a similar trend was also observed in the other studies.

Choosing between using a NOAC or VKA

High quality anticoagulation control with VKAs is associated with better efficacy and safety (with low stroke and bleeding risks), and thus, effective stroke prevention in various guidelines with oral anticoagulation refers to use of well-controlled warfarin (TTR ≥70%) or one of the NOACs[22]. Whilst NOACs generally offer many advantages, a clinical dilemma is how to predict those newly diagnosed non-anticoagulated AF patients who would do well on VKA achieving a high TTR, especially given costs of the NOACs and given that the benefits of NOACs over VKAs may be only marginal in those with high TTRs. An ESC position paper[5] recommends use of the new SAMe-TT_2R_2 score[9] to aid decision-making by identifying those AF patients likely to do well on warfarin (SAMe-TT_2R_2 score 0-1) or those more likely to have poor anticoagulation control (SAMe-TT_2R_2 score>2). Those patients with a SAMe-TT_2R_2 score>2 would probably be better off being started on NOACs as initial therapy, or be targeted for more efforts to improve their anticoagulation control.

Specific patient groups

Renal dysfunction

Patients with AF and renal impairment are at high risk of stroke/thromboembolism, bleeding, myocardial infarction and death.[23,24,25,26] Nonetheless, the net clinical benefit seems to favour use of oral anticoagulation, rather than no anticoagulation. Given the age and comorbidities associated with AF, the presence of normal renal function or even mild renal impairment at baseline does not preclude some patients deteriorating to severe renal impairment.[27]

Renal impairment might influence the balance between the safety and efficacy of NOACs (**Figure 1**). The various NOACs have different renal elimination characteristics, and this issue may affect the choice of a specific agent. Dabigatran is the drug that is most dependent on the renal function for its elimination and the risk for major bleeding increases with decreasing renal function. For dabigatran 110 mg the annual event rate was 1.53%, 2.89%, and 5.29% for CrCl≥80, 50–79, and <50 mL/min, respectively, and for the 150 mg dose the corresponding event rates were 2.09%, 3.33%, and 5.44%, respectively.[28] Thus, exposure to dabigatran is increased by renal impairment, and this correlates with the severity of renal dysfunction. Despite a dose reduction, drug accumulation and overdose were initially reported in elderly patients with a low body weight and moderate renal insufficiency, which led to severe and fatal bleeding complications.[29] In those with moderate renal impairment, the lower dose of dabigatran (110 mg) should be used with regular monitoring of renal function.[28,30] A RE-LY sub-analysis[31] has demonstrated that the efficacy of both dosages of dabigatran was consistent with the overall trial irrespective of renal function, and the relative reduction of major bleeding with either dabigatran dose compared to warfarin was greater in patients with GFR ≥80 mL/min.

The excretion of rivaroxaban and apixaban is only partly dependent upon renal function, and the risk of drug accumulation in patients with renal insufficiency is lower than that observed with dabigatran (**Figure 1**). For rivaroxaban, the event rate was 2.06% for a CrCl ≥80 mL/min, 2.77% for a CrCl 50–79 mL/min, and 3.37% for CrCl<50 mL/min.[16] For apixaban, the event rate was 1.5%, 2.5%, and 3.2% for normal renal function, mild impairment, and moderate-severe impairment, respectively.[17] Both drugs can be administered at fixed doses in patients with moderate renal impairment, and the current prescribing label for both drugs allows its use if creatinine clearance is ≥15 mls/min. For apixaban, a recent analysis clearly shows the safety of this drug with moderate renal impairment, whilst retaining superior efficacy.[32] Although the ENGAGE AF-TIMI 48trial has yet to formally publish data regarding the event rate of bleeding in patients with renal impairment, edoxaban is also partly dependent on renal function (50% renal excretion).

In summary, we should check renal function in all patients before choosing one of the NOACs and should not give any NOACs to patients with severe renal impairment (CrCl< 30 mL min). In patients with moderate renal impairment (CrCl 30–50 mL min),although dabigatran 110 mg bid and rivaroxaban can be used, apixaban is probably the safer option, particularly in elderly patients with a low body weight (<60kg).

Elderly patients

While AF is uncommon in patients below 65 years of age (<2%), the prevalence is approximately 10% in patients aged 85 years or over.[33] Due to the higher incidence of stroke in the elderly, the absolute risk reduction is higher in elderly than in younger patients.[34] Oral anticoagulation is beneficial in the elderly with a superior reduction in stroke and no significant difference in major bleeding between warfarin and aspirin.[35]

Regardless of high stroke risk and a greater net clinical benefit from oral anticoagulation, elderly patients with AF (aged >75–80 years) are often denied warfarin owing to the perception of a substantially increased bleeding risk in the presence of multiple comorbidities, impaired renal function, or cognitive impairment.[36] However, due to a lower tendency for food and drug interactions, the anticoagulant effects of NOACs are much more predictable than VKAs, allowing them to be given in fixed doses without routine coagulation monitoring.

The NOACs have many benefits over warfarin for stroke prevention in patients with AF in the elderly. Treatment decisions also require an assessment of the practical considerations associated with these treatments, including the need for dose adjustment in specific patients, cost-effectiveness, limitations in monitoring the extent of anticoagulation, and the lack of specific reversal agents. Such considerations are particularly important in the treatment of older patients, who may experience different reactions to drugs than younger patients. This is often due to older patients having poor renal clearance, a lower body weight, and polypharmacy.[37]

Data from the phase III randomized, controlled trials all confirm that the absolute risks of both thrombotic events and bleeding rise with advancing age. For instance, patients aged over 75 years represented 43.1%, 31.2%, 40.2%, and 40.1% in the ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48, and RE-LY studies, respectively. In ROCKET-AF, the efficacy and safety of rivaroxaban appears to be consistent across age categories. In the various trials with rivaroxaban, apixaban and edoxaban, no interaction with age was reported for the efficacy outcome and the occurrence of major bleeding. In the RE-LY study, however, a highly significant interaction between age and major bleeding was found (**Figure 2**).

Racial differences

The age-adjusted prevalence of AF may be lower among Asians than among Caucasians.[33] However, the prevalence and incidence of arterial thromboembolism may differ from those of European and American countries.[38] Specifically, Asian patients have a five-to-six-fold higher stroke risk than Caucasians, but anticoagulation therapy is not commonly given to Asian patients with non-valvular AF, probably because of the (perceived) risk of critical bleeding, which might be higher in Asian patients. Indeed, warfarin-related intracranial hemorrhage in Asian patients was reported to be 1.75 per 100 patient-years, which is significantly higher than that in Caucasians (0.34 per 100 patient-years).[39] This is further complicated by the difficulty of maintaining a therapeutic international normalized ratio when using VKAs. These challenges might explain why VKAs are underused by physicians who treat patients in Asia.[40]

Moreover, in Asians, the risk of stroke and systemic embolism for warfarin-anticoagulated AF patients appears to be higher compared to Non-Asians, though Asians had similar mean $CHADS_2$ scores.[41] Indeed, in the RE-LY Asia sub-analysis[42], although the mean $CHADS_2$ score was 2.2 in Asian countries (2.1 in Non-Asians), the incidence rate of stroke and systemic embolism was much higher in Asians compared to Non-Asians (3.06%/year vs 1.48%/year). In the ROCKET-AF East Asia sub analysis[16], although the mean $CHADS_2$ score of 3.2 in East Asian countries (3.5 in Non-East Asians), the incidence rate of stroke and systemic embolism was higher in East Asians compared to Non-East Asians (3.4%/year vs 2.4%/year). In the ARISTOTLE trial[17,43], although the mean $CHADS_2$ score was 2.1 in Asian countries (2.1 in non-East Asians), the incidence rate of stroke and systemic embolism was higher in Asians compared to Non-Asians (3.39%/year vs 1.38%/year). Also, in these trials, the TTR was generally lower in Asians compared to non-Asians (RELY; 56.5% in Asians vs 68.9% in Non-Asians, ROCKET AF; 52.4% vs 55.2%, ARISTOTLE; 60% vs 67%). These data would suggest that trial investigators in Asia tended to keep an INR in the lower range, perhaps to avoid bleeding. Both bleeding and thromboembolism rates are generally higher in Asians compared to non-Asians, and therefore warfarin is difficult to manage properly in Asians.

The NOACs may provide a safe, effective, and convenient alternative to warfarin, especially in Asians (the Asian sub-analysis of edoxaban are awaited). The Asian subgroup analysis of the RE-LY trial demonstrated superiority of dabigatran 150 mg bid over warfarin in reducing thromboembolism. Also, the risk of major bleeding in the group of dabigatran 150 bid was significantly lower than the warfarin group in Asians, with a greater relative risk reduction than

that from non-Asians. Indeed, the annual risk of major bleeding in dabigatran 150 mg bid group was 2.17% for Asians and 3.52% for non-Asians. The annual risk of major bleeding in dabigatran 110 mg bid group was 2.22% in Asians and 2.99% in non-Asians. In the Asian sub-group analysis of the ARISTOTLE trial[43], apixaban had consistent benefits when compared with warfarin for stroke or systemic embolism in East Asian and non-East Asian patients. The annual risk of major bleeding from apixaban was 2.02% for Asians and 2.15% for non-Asians. The rate of stroke and systemic embolism from the East Asia cohort of the ROCKET-AF study were consistent with those of the main study. The annual risk of major bleeding from rivaroxaban was 4.9% for Asians and 7.6% for non-Asians.

The use of NOACs in patients with AF in Asia provides an opportunity for improved quality of care, since the rate of both thromboembolism and bleeding risk associated with NOACs was consistent with that observed globally. A modeling exercise suggests how use of NOACs may lead to a major impact on the burden of AF-related stroke in China.[44]

Combination of non-VKA oral anticoagulants and antiplatelet therapy

The management of antiplatelet and anticoagulant therapy is challenging in patients with AF who sustain an acute coronary syndrome and/or undergo percutaneous coronary intervention/stenting, or in patients with coronary artery disease who develop AF. The optimal strategy to provide adequate antiplatelet and anticoagulant therapy is currently unclear.

Observational data have shown an increased risk of bleeding after treatment with antiplatelet therapy together with an anticoagulant "triple therapy."[45,46] A sub-analysis of the RE-LY trial showed an increased risk of bleeding and thromboembolic events associated with antiplatelet therapy compared with no antiplatelet therapy and consistent treatment effects when compared with warfarin, regardless of aspirin use.[47] Both the ATLAS ACS 2-TIMI 51[48] and APPRAISE-2[49] trials confirmed a dose-dependent increase in major bleeding events, including intracranial bleeding, with rivaroxaban and apixaban when they were combined with dual antiplatelet therapy (DAPT).

In the ATLAS ACS 2-TIMI 51, low-dose (2.5 mg bid) rivaroxaban was associated with a significantly lower composite of cardiovascular death, myocardial infarction, or stroke (the primary efficacy endpoint), compared to placebo. Of note, the doses were 2.5 or 5 mg bid, which correspond to one-fourth and one-half, respectively, of the dose tested in AFpatients.[16] In APPRAISE-2, however, the primary safety outcome of major bleeding occurred more often with apixaban than with the placebo. Apixaban was associated with more intracranial hemorrhage and with a numerical increase in fatal bleeding. Consequently, the trial was terminated prematurely before completing enrollment of the planned patients considering the overall efficacy/safety balance.

In summary, the need for NOACs in combination with DAPT should be critically assessed, and the duration of combined therapy minimized. The duration of DAPT is determined by the risk of

bleeding, type of stent and the perceived risk of stent thrombosis. The use of third-generation drug eluting stents may reduce the time DAPT is required to prevent stent thrombosis.

Patient's values and preferences

Patient's preferences for OAC therapy should be an integral part of the treatment decision-making process,[50] as advocated by current clinical guidelines.[22] To enable patients to make informed choices about whether or not to initiate OAC and to allow them to choose between the available OAC drugs requires the patient to be appropriately educated about their own individual risk of stroke (hence the need for OAC) and their risk of major bleeding associated with the different OACs. The responsibility for educating AF patients and allowing them to voice their preferences for OAC treatment lies with the treating clinician.[51] A recent study by LaHaye and colleagues[52] used an iPad to present patients with their individual risk of stroke (using CHA_2DS_2-VASc) and bleeding with treatment, using a variety of different formats and elicited their preferences for antithrombotic therapy. This study corroborates previous research[50] which reports that patients are more concerned about the risk of stroke than the risk of bleeding; patients were prepared to suffer 4.4 major bleeds in order to prevent one stroke.[52] Involving patients' in discussions about treatment options and eliciting their preferences provides clinicians with the opportunity to educate patients about AF and the risks and benefits of treatment, to correct or allay misconceptions patients may hold about OAC, identify and overcome barriers to adherence, and improves the likelihood of arriving at a mutually agreeable treatment decision.[51]

Conclusion

This overview has several limitations. First, each phase III trial examined different NOACs and there was important heterogeneity regarding study designs and included populations. Second, patients taking warfarin in real-life clinical practice are less likely to be in a therapeutic range than those in controlled studies. Therefore, further insights into the appropriate use of these agents will become apparent when they are used in 'real-world' clinical settings, and some initial data from post-marketing studies do suggest that these drugs appear safe compared to warfarin when used in newly diagnosed anticoagulation naïve patients.[53,54] Some reports suggest need for caution amongst 'switchers' from warfarin to NOACs, and a high rate of bleeding and thromboembolism was observed.[55] It is worth emphasizing that these drugs are powerful anticoagulants that offer efficacy and safety compared to warfarin if used correctly according to guidelines and/or prescribing recommendations.[56]

The introduction of 4 new NOAC alternatives for anticoagulation represents a major step forward in improving outcomes and quality of life. Compared with VKAs, these new alternatives have important advantages, such as lower risk of intracranial bleeding, no clear interactions withfood, favorable pharmacokinetic profiles, and no need for routine monitoring. Indeed, these new oral anticoagulants will be preferred alternatives to VKAs for many patients with AF and an increased risk of stroke. Modelling analyses clearly show the potential healthcare and public health impact of NOACs in reducing the burden of stroke in patients with AF.[57,58] Things can only get better.

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Figure legends

Figure 1. Forest plot for major bleeding according to creatinine clearance (CCr), non-VKA oral anticoagulants (NOACs) versus warfarin in patients with nonvalvular AF

D 150:dabigatran 150mg bid, D 110:dabigatran 110mg bid

Figure 2. Forest plot for major bleeding according to age, non-VKA oral anticoagulants (NOACs) versus warfarin in patients with nonvalvular AF

D 150:dabigatran 150mg bid; D 110:dabigatran 110mg bid

Edoxabanhigh:edoxaban 60mg od, Low:edoxaban 30mg od

Table 1: Characteristics of NOAC

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Target	Xa	Xa	Xa	IIa
Pro-drug	No	No	No	Yes
Oral bioavailability	80-100%	50%	62%	6.5%
Half-life (h)	8-11	12	10-14	12-14
Interaction	3A4/P-gp	3A4/P-gp	P-gp	P-gp
Renal clearance	33% kidney 66% liver	25%	50%	80%
Regimen	Once*	Twice	Once	Twice*
Dose adjustment for patients	CrCl 30-49ml/min	fulfilling ≥2 of the following criteria at baseline: ◆ Age ≥80 years ◆ Body weight ≤60 kg ◆ Serum creatinine ≥1.5mg/dl	fulfilling ≥1 of the following criteria at baseline: ◆ Concomitant verapamil or quinidine ◆ Body weight ≤60 kg ◆ CrCl 30–50 ml/min	No dose adjustment
Dose	20mg→15mg	5mg→2.5mg	60mg→30mg 30mg→15mg	No dose adjustment

*Depend on indicate

Table 2: Clinical study design of NOAC

- Definition of Major bleeding-

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Trial	ROCKET AF	ARISTOTLE	ENGAGE AF	RE-LY
Primary safety	Major Bleeding （ISTH） NMCR Bleeding	Major Bleeding （ISTH）	Major Bleeding (modified ISTH)	Major Bleeding
Major Bleeding	• A decrease in Hb level of ≥2 g/dl • A transfusion of ≥2 U of packed red blood cells or whole blood • Fatal bleeding • Critical organ bleeding	• A decrease in Hb-level of ≥2 g/dl over a 24-hour period • A transfusion of ≥2 U of packed red blood cells • Fatal bleeding • Critical organ bleeding	• A decrease in Hb-level of ≥2 g/dl • A transfusion of ≥2 U of packed red blood cells • Fatal bleeding • Symptomatic critical organ bleeding	• Reduction in Hb level of ≥2 g/dl • Transfusion of ≥2 U of blood • Fatal bleeding • Symptomatic critical organ bleeding

NMCR:non-major clinically relevant bleeding

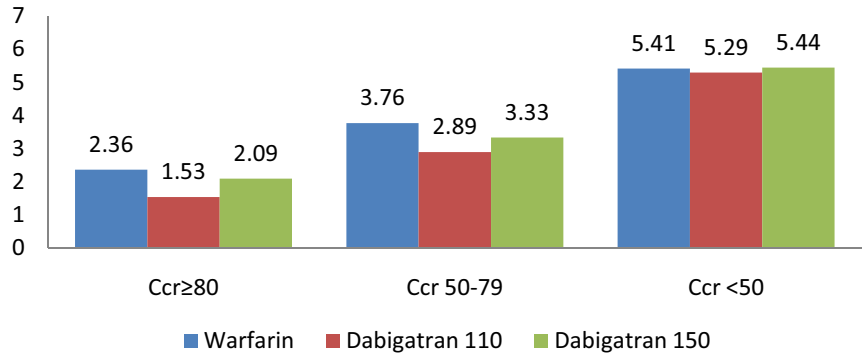
Table 3: Phase III studies of NOAC

Trial	ROCKET AF	ARISTOTLE	ENGAGE AF		RE-LY	
Drug	Rivaroxaban 20mg vs warfarin	Apixaban 5mg vs warfarin	Edoxaban 60mg vs warfarin	Edoxaban 30mg vs warfarin	Dabigatran 150mg vs warfarin	Dabigatran 110mg vs warfarin
Patients	14,264	18,201	21,105		18,113	
Age years	Median 73	Median 70	Median 72		Mean 72	
Prior stroke, TIA	55%	19%	28%		20%	
Blindness	DBT	DBT	DBT		Open (PROBE)	
CHADS2 (result)	≥2 (3.5)	≥1 (2.1)	≥2 (2.8)		≥0 (2.1)	
VKA naive	38%	43%	41%		50.4%	
TTR (mean)	55%	62%	65%		64%	
Efficacy	ITT	ITT	ITT		ITT	
Stroke or systemic embolism (%/year; HR; 95%CI)	2.12% vs2.42%; 0.88; 0.75-1.03; P for non-inferiority<0.001, P for superiority p=0.12	1.27% vs1.60%; 0.79; 0.66-0.95; p=0.01	1.57% vs 1.80%; 0.87;0.73-1.04; P=0.08	2.04% vs 1.80%; 1.13;0.96-1.34; P=0.10	1.11% vs1.71%; 0.65; 0.52-0.81; p<0.001	1.54 % vs 1.71% 0.90 ; 0.74-1.10; p=0.30
Ischaemic stroke	1.34% vs1.42%; 0.94; 0.75-1.17; p=0.581	0.97% vs 1.05%; 0.92; 0.74-1.13; p=0.42	1.25% vs 1.25%; 1.00 ;0.83–1.19; P=0.97	1.77% vs 1.25%; 1.41;1.19–1.67; P<0.001	0.92% vs 1.21%; 0.76; 0.59-0.97; p=0.03	1.34% vs 1.21%; 1.11; 0.89-1.40; p=0.35

Haemorrhagic stroke	0.26% vs0.44%; 0.59; 0.37-0.93; p=0.024	0.24% vs 0.47%; 0.51; 0.35-0.75; p<0.001	0.26% vs 0.47%; 0.54;0.38–0.77; P<0.001	0.16% vs 0.47%; 0.33;0.22–0.50; P<0.001	0.10% vs 0.38%; 0.26; 0.14-0.49; p<0.001	0.12% vs 0.38%; 0.31; 0.17-0.56;p<0.001
All cause mortality	1.87% vs 2.21%; 0.85; 0.70-1.02; p=0.073	3.52% vs 3.94% 0.89; 0.80-0.998; p=0.047	3.99% vs 4.35% 0.92;0.83–1.01; P=0.08	3.80% vs 4.35%; 0.87;0.79–0.96; P=0.006	3.64% vs 4.13%; 0.88; 0.77-1.00; p=0.051	3.75% vs 4.13%; 0.91; 0.80-1.03; p=0.13
Safety	On treat	On treat	On treat	On treat	ITT	
Major bleeding	3.6% vs 3.45%; not specified; p=0.576	2.13% vs 3.09%; 0.69; 0.60-0.80; p<0.001	2.75% vs 3.43%; 0.80;0.71–0.91; P<0.001	1.61% vs 3.43%; 0.47;0.41–0.55; P<0.001	3.32% vs 3.57%; 0.93; 0.81-1.07; p=0.31	2.87 % vs 3.57%; 0.80; 0.70-0.93; p=0.003
Intracranial bleeding	0.49% vs 0.74%; 0.67; 0.47-0.93; p=0.019	0.33% vs 0.80%; 0.42; 0.30-0.58; p<0.001	0.39% vs 0.85%; 0.47;0.34–0.63; P<0.001	0.26% vs 0.85%; 0.30;0.21–0.43; P<0.001	0.30% vs 0.76%; 0.41; 0.28-0.60; p<0.001	0.23% vs 0.76%; 0.30; 0.19-0.45; p<0.001

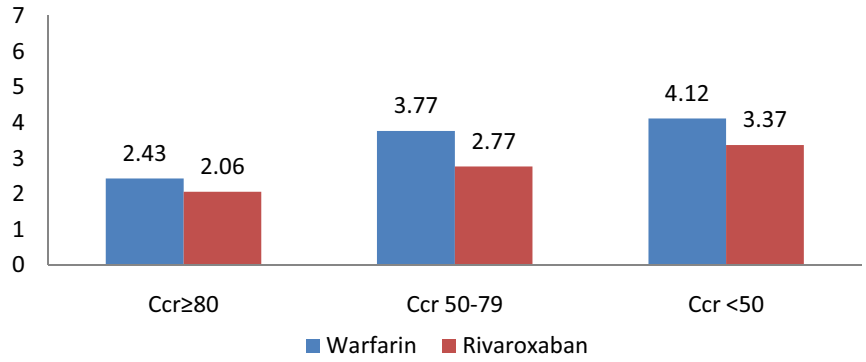
Figure 1 Major bleeding rate (%/year) according to creatinine clearance (CCr)

Dabigatran versus warfarin



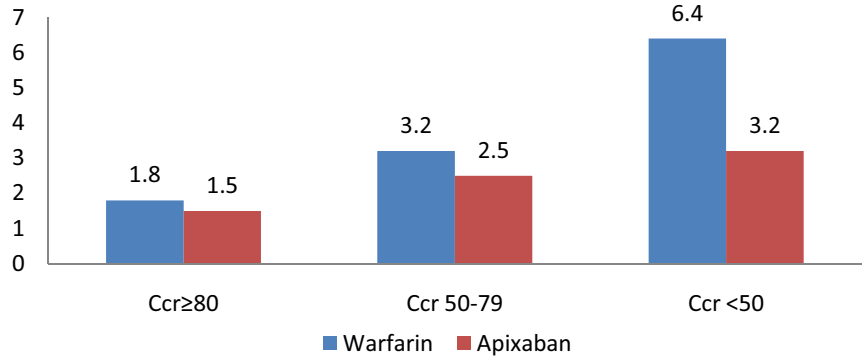
P Value for interaction
Dabigatran 110 vs warfarin P=0.12
Dabigatran 150 vs warfarin P=0.68

Rivaroxaban versus warfarin



P Value for interaction
Rivaroxaban vs warfarin P=0.715

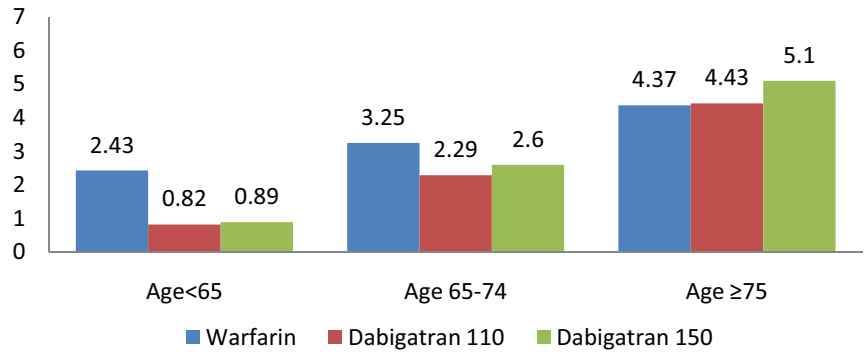
Apixaban versus warfarin



P Value for interaction
Apixaban vs warfarin P=0.03

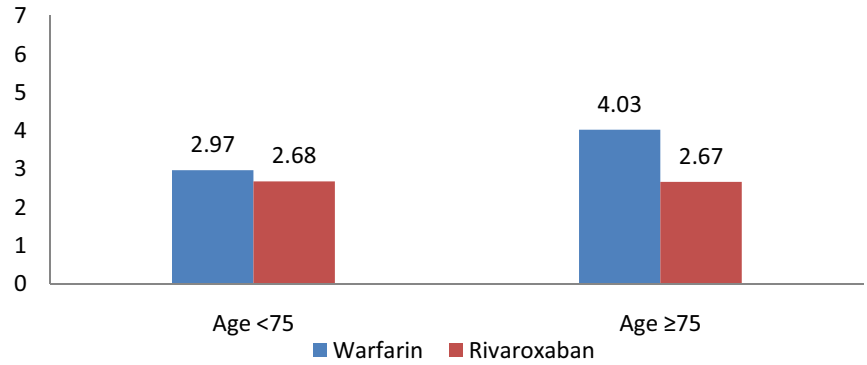
Figure 2 Major bleeding (%/year) according to age

Dabigatran versus warfarin



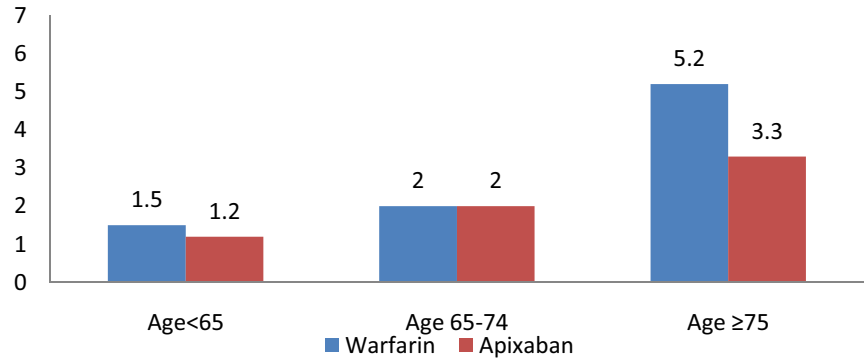
P Value for interaction
Dabigatran 110 vs warfarin P=0.003
Dabigatran 150 vs warfarin P=0.001

Rivaroxaban versus warfarin



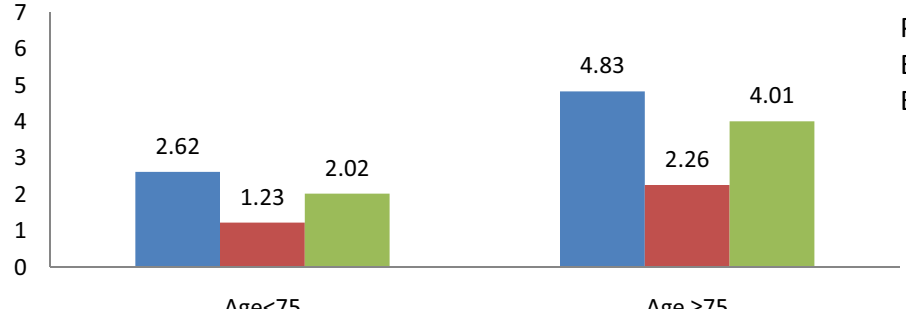
P Value for interaction
Rivaroxaban vs warfarin P=0.107

Apixaban versus warfarin



P Value for interaction
Apixaban vs warfarin P=0.64

Edoxaban versus warfarin



P Value for interaction
Edoxaban 30 vs warfarin P=0.95
Edoxaban 60 vs warfarin P=0.57