Stroke prevention in atrial fibrillation: do we still need warfarin?

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Purpose of review
Oral anticoagulation with vitamin K antagonists (warfarin, phenprocoumon) is successful in both primary and secondary stroke prevention in patients with atrial fibrillation, yielding a 60–70% relative reduction in stroke risk compared with placebo, as well as a mortality reduction of 26%. However, these agents have a number of well documented shortcomings. Acetylsalicylic acid (ASA) reduces the relative risk of stroke by a nonsignificant 19% compared with placebo, and increased bleeding risk offsets any therapeutic gain from the combination of ASA with clopidogrel. This review describes the current landscape and developments in stroke prevention in patients with atrial fibrillation, with special reference to secondary prevention.

Recent findings
A number of new drugs for oral anticoagulation that do not exhibit the limitations of vitamin K antagonists are under investigation. These include direct factor Xa inhibitors and direct thrombin inhibitors. Recent studies (RE-LY, ROCKET-AF, AVERROES, ARISTOTLE) provide promising results for new agents, including higher efficacy and significantly lower incidences of intracranial bleeds compared with warfarin. The new substances show similar results in secondary as in primary stroke prevention in patients with atrial fibrillation.

Summary
New anticoagulants add to the therapeutic options for patients with atrial fibrillation, and offer a number of advantages over warfarin, for both the clinician and patient, including a favourable bleeding profile and convenience of use. Consideration of these new anticoagulants will improve clinical decision making.

Keywords
apixaban, atrial fibrillation, dabigatran, rivaroxaban, stroke, warfarin

INTRODUCTION

Atrial fibrillation is a significant risk factor for cardioembolic stroke [1], and is responsible for approximately 25% of all ischemic strokes [2]. The median age of patients with atrial fibrillation in Western countries is approximately 72 years [3]. Atrial fibrillation is becoming increasingly prevalent as populations get older, and by the year 2050 it is projected to affect 5.6 million US adults, of whom more than 50% will be over 80 years of age [4].

Patients with atrial fibrillation have a four-fold to five-fold higher risk of ischemic stroke than those without atrial fibrillation [1]. The risk of atrial fibrillation-related stroke also increases with age, with a 1.5-fold increase per decade [5▪]. Furthermore, the risk of stroke for patients who have already experienced a stroke or transient ischemic attack (TIA) is reported to be 2.5 times greater than for patients who have not [5▪]. A meta-analysis of stroke prevention in atrial fibrillation trials found an average stroke rate of 13% per year in untreated atrial fibrillation patients with prior stroke or TIA compared with 4.1% per year in atrial fibrillation patients with no history of stroke/TIA [6]. In the Copenhagen Stroke Study mortality was doubled for recurrent strokes, emphasizing the importance of anticoagulation for secondary prevention [7].

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KEY POINTS

- Patients with atrial fibrillation are at high risk of stroke. The stroke risk is increased in patients with atrial fibrillation who have already suffered a transient ischemic attack or stroke.
- The risk of stroke is dramatically decreased by prevention with oral anticoagulants. Vitamin K antagonists have many shortcomings, which explain that only about 50% of all patients with atrial fibrillation and without contraindications are treated with warfarin or phenprocoumon.
- The new oral anticoagulants are at least as effective, or more effective than vitamin K antagonists in the prevention of stroke and systemic embolism in patients with atrial fibrillation.
- All new anticoagulants result in a significant decrease in intracranial bleeding complications compared with warfarin.
- Apixaban is superior to aspirin in patients with atrial fibrillation regarded unsuitable for treatment with vitamin K antagonist, with a similar rate of major bleeding complications.

The purpose of this review is to discuss stroke prevention in atrial fibrillation patients with vitamin K antagonists (VKAs) with special reference to secondary stroke prevention. We will then discuss the results of recently completed treatment trials with the new oral anticoagulants. The future will show whether the new anticoagulants will replace VKAs, and whether well controlled patients on warfarin with stable INR will remain on this drug.

SECONDARY PREVENTION WITH WARFARIN

Warfarin, the most commonly used oral VKA, was introduced over 60 years ago to prevent deep vein thrombosis and strokes. Over the last 20 years, there have been a number of randomized controlled studies in which patients with atrial fibrillation were treated with warfarin or placebo. In a meta-analysis of stroke prevention in atrial fibrillation trials by Hart *et al.* [6], warfarin was associated with a 64% (95% CI 49–74) reduction in stroke compared with placebo or no intervention, and a 37% (95% CI 23–48) reduction compared with antiplatelet therapy.

Until recently, there had been only one study that focused exclusively on secondary prevention in patients with permanent, persistent and paroxysmal atrial fibrillation – the European Atrial Fibrillation Trial (EAFT), which involved patients with TIAs or minor strokes and compared warfarin (target INR 3.0, range 2.5–4.0) and acetylsalicylic acid (ASA; 300 mg/day) with placebo [8▪]. The study comprised 1007 patients with atrial fibrillation who were observed for an average of 2.3 years. In those patients considered eligible for VKAs, warfarin provided a highly significant 66% relative risk (RR) reduction in all stroke compared with placebo (HR 0.34, 95% CI 0.20–0.57; $P < 0.001$). In comparison with ASA, it also provided a significant RR reduction of 62% (HR 0.38, 95% CI 0.23–0.64; $P < 0.001$). The incidence of major bleeding complications on treatment was 2.8% per year with warfarin, and 0.9% per year with ASA [8▪]. The meta-analysis by Hart *et al.* [6] found that, compared with placebo or no intervention, warfarin was associated with an absolute risk reduction of 2.7% per year for primary prevention, rising to 8.4% per year for secondary prevention. Also, compared with ASA, the absolute risk reduction with warfarin was 0.7% per year for primary prevention, but 7.0% per year for secondary prevention.

A study of 13 599 patients with atrial fibrillation over 6 years found that, although prior ischemic stroke was the strongest risk factor for stroke and systemic embolism, it was also one of the strongest risk factors for intracranial haemorrhage [9]. While receiving warfarin the annual rate of thromboembolism was 1.09 per 100 person years in patients with no history of stroke, and 3.46 per 100 person years in patients with a history of stroke. The annual rates of intracranial haemorrhage during warfarin therapy were 0.51 in patients with no history of stroke compared with 1.16 in patients with prior stroke. Despite the increased bleeding risk an assessment of net clinical benefit (annualized rate of thromboembolic events minus 1.5 times the annualized rate of intracranial haemorrhage) found that the benefit of warfarin administration in patients with a history of stroke was more than four-fold higher, compared with patients with no prior stroke (2.48 versus 0.56% per year).

Problems associated with vitamin K antagonists

Warfarin inhibits the synthesis of coagulation factors II, VII, IX and X, and is metabolized by the cytochrome P450 enzyme complex [10,11]. As a consequence, it exhibits a large range of interactions with other drugs, interactions that are not limited to those that also influence the coagulation system. The effects of warfarin also depend on liver function, genetic factors, alcohol consumption, food and, above all, patient compliance [10]. Warfarin has a relatively narrow therapeutic window of INR values

between 2.0 and 3.0. INR values below 2.0 are associated with insufficient anticoagulation, and a subsequent rise in the risk of ischemic strokes, although INR values in excess of 4.0 increase the risk of intracranial bleeding substantially [12,13]. There is also a range of contraindications and precautions for warfarin use, including the state of the patient's health after major surgery, various bleeding complications, malignant hypertension, and senility in unsupervised patients. Warfarin therapy is often discontinued. Data from the Swedish Stroke Registry showed that, of stroke survivors discharged from hospital on warfarin therapy, only 45% were persistent users 2 years later [14].

Medicare data collected from 1992 to 2002 indicate an increased use of warfarin in patients with atrial fibrillation, achieving a 56.3% rate in 2002 [15]. The increased use of warfarin was associated with a decrease in ischemic stroke, but unchanged rate of haemorrhagic stroke. Despite the convincing evidence of the efficacy of VKAs in stroke prevention, these drugs remain underused in most countries. Reasons include the need for regular coagulation checks (INR control), real or perceived contraindications, and the fear of major bleeding complications, in particular intracranial bleeds [16,17].

Stroke prevention in patients with atrial fibrillation needs to balance benefit (prevention of ischemic stroke) versus risk (major bleed including intracranial bleed). Whereas patients are usually afraid of a stroke, physicians are often afraid of bleeding complications. This results in an underuse of anticoagulation therapy as shown in a systematic review of 54 studies [18]. Up to 40% of patients who had a TIA or an ischemic stroke were not treated with an oral anticoagulant for secondary prevention.

Although warfarin has proven efficacy for stroke prevention in atrial fibrillation, its limitations and associated risk of bleeding indicate that there is a clear need for an alternative to VKAs. The ACTIVE W study compared the combination of ASA and clopidogrel with VKAs for prevention of vascular events in patients with atrial fibrillation [19]. This study was terminated early by the Data and Safety Monitoring Board, after it became clear that the combination of the two antiplatelet drugs led to a 44% increase in the RR for embolic events, including strokes, compared with VKAs. Surprisingly, the combination of clopidogrel and ASA did not lead to the expected lower rate of major bleeding complications compared with warfarin. There were significant differences between patients who had already been on oral anticoagulation prior to study enrolment versus patients who were treated *de novo*. Patients who were on warfarin at study entry had a lower discontinuation rate, a better INR control, and a smaller difference in primary outcome event rates between warfarin and aspirin plus clopidogrel compared with patients starting on warfarin at study entry.

The ACTIVE A study compared clopidogrel and ASA combination therapy with ASA alone in atrial fibrillation patients who had contraindications to warfarin, or had declined treatment with warfarin [20]. A total of 13.1% of the 7554 patients had already suffered a stroke or TIA. The combination of clopidogrel and ASA was better at preventing ischemic strokes compared with ASA alone [21]. However, the combination also caused a higher rate of bleeding complications. If 1000 patients were treated for 1 year, the combination of clopidogrel and ASA would prevent nine ischemic strokes, and would result in seven instances of major bleeding compared with ASA alone.

Summarizing the evidence from randomized trials there is overwhelming evidence that VKAs are superior to ASA, and the combination of ASA plus clopidogrel. The combination of ASA and clopidogrel is superior to ASA monotherapy, but carries a higher risk of major bleeding complications.

NEW ANTICOAGULANTS

The new anticoagulants described in detail below share common properties such as high specificity, fixed oral dosing, no interaction with food, few interactions with other drugs, no need for anticoagulation monitoring, and rapid onset and offset of action. The major phase III trials which are ongoing or completed are shown in Table 1.

Oral direct thrombin inhibitors

Dabigatran (Pradaxa), developed by Boehringer Ingelheim, is a competitive and reversible direct thrombin inhibitor, administered orally as a prodrug, dabigatran etexilate [22,23]. Dabigatran has a predictable coagulation-inhibiting effect without interacting with food, although food does delay the time to maximal absorption by approximately 2 h [24,25]. Around 80% of systemically available dabigatran is eliminated via the kidneys [26].

The CYP3A4 isoenzyme is not involved in dabigatran's metabolism, although there is a chance of interaction with drugs that are metabolized by this route (such as atorvastatin) [27]. Dabigatran interacts with amiodarone, quinidine, ketoconazole and verapamil. The interaction, however, does not require dose adjustments according to the US Food and Drug Administration (FDA). The European label

Table 1. Overview of completed and ongoing phase III trials of new anticoagulants in patients with atrial fibrillation

Study acronym	Drug	Inclusion criteria and patients	Primary outcome	Result	Comments
RE-LY [30▪▪]	Dabigatran 110 mg or 150 mg b.i.d. Warfarin INR 2–3	18 113 patients with atrial fibrillation and at least one risk factor for stroke	Stroke, systemic embolism	110 mg dabigatran noninferior, 150 mg dabigatran superior to warfarin	110 mg dabigatran approximately 70% decrease and 150 mg dabigatran approximately 60% decrease in intracranial bleeds
ROCKET-A F [48▪▪]	Rivaroxaban 20 mg o.d.[a] Warfarin INR 2–3	14 264 patients with atrial fibrillation and prior stroke/TIA/systemic embolism or at least two risk factors for stroke	Stroke, systemic embolism	Rivaroxaban noninferior in ITT analysis, superior in PP analysis	Double-blind, high proportion of patients with prior stroke
ARISTOTLE [49▪▪]	Apixaban 5 mg b.i.d.[b] Warfarin INR 2–3	18 201 patients with atrial fibrillation or flutter, at least one risk factor for stroke	Stroke, systemic embolism	Apixaban superior to warfarin in ITT analysis	Double-blind
ENGAGE-AF-TIMI 48 [58]	Edoxaban 30 mg or 60 mg o.d. Warfarin INR 2–3[c]	>20 000 patients with atrial fibrillation, moderate or high risk	Stroke, systemic embolism	Study results expected in spring 2012 (ClinicalTrials.gov 2010c)	Double-blind
AVERROES [59]	Apixaban 5 mg b.i.d. Aspirin 81–324 mg	5599 patients with atrial fibrillation unsuitable for VKA therapy	Stroke, systemic embolism	Apixaban superior to ASA (RRR 55%)	Equivalent rate of major bleeds

ASA, acetylsalicylic acid; VKA, vitamin K antagonist.
[a]15 mg once daily (o.d.) in patients with creatinine clearance (CrCl) 30–49 ml/min.
[b]2.5 mg twice daily (b.i.d.) in patients with two of: age 80 years; body weight <60 kg; serum creatinine 1.5 mg/dl (133 μmol/l).
[c]50% dose reduction for patients with anticipated elevated exposure (one of CrCl 30–50 ml/min; body weight ≤60 kg; concomitant verapamil or quinidine).

recommends use of the low dose of 110 mg twice daily (b.i.d.) in patients on verapamil (http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf). The concomitant use of dabigatran and rifampicin, as well as ketoconazole, should be avoided. As dabigatran is primarily eliminated renally, the EU label indicates severe renal impairment [creatinine clearance (CrCl) less than 30 ml/min] as a contraindication. However, the FDA have approved a lower 75 mg b.i.d. dose for patients with a CrCl of 15–30 ml/min (Pradaxa US prescribing information 2011, http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf).

Dabigatran in stroke prevention in patients with atrial fibrillation

In an initial dose finding study in patients with atrial fibrillation, the so-called PETRO study, 502 patients documented as having atrial fibrillation with coronary artery disease plus at least one additional risk factor were given three different doses of dabigatran etexilate – 50, 150 and 300 mg b.i.d. or warfarin at a target INR between 2.0 and 3.0 [28]. These were a mixed group of patients receiving ASA (81 or 325 mg/day) and those not receiving ASA. The primary endpoint was bleeding complications. The study showed that patients receiving 50 mg of dabigatran etexilate b.i.d. were possibly underdosed, and that 300 mg of dabigatran etexilate b.i.d. (particularly in those also receiving ASA) was associated with a high risk of bleeding complications. Based on these results and pharmacokinetic modelling, doses of 110 and 150 mg b.i.d. dabigatran were chosen for the phase III programme.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial was a large international, multicenter, randomized trial that included 18 113 patients with nonvalvular atrial fibrillation, and at least one additional risk factor for stroke [29,30▪▪]. Patients were randomized 1 : 1 : 1 to receive one of two blinded doses of dabigatran, either 110 mg b.i.d. (1195 had prior stroke, and 4820 had no prior stroke), or 150 mg b.i.d. (1233 had prior stroke, and 4843 had no prior stroke), or open-label warfarin (INR 2.0–3.0; 1195 had prior stroke, and 4827 had no prior stroke). The median follow-up period was 2 years, and those with severe renal insufficiency (CrCl less than 30 ml/min) were excluded from study participation. Events were blinded and independently adjudicated following a PROBE design (prospective randomized open with blinded endpoint evaluation). The primary

outcome was the composite of stroke or systemic embolism [29].

The primary outcome event rates were 1.71% per year in the warfarin group, and 1.54% per year in the dabigatran 110 mg group (RR with dabigatran, 0.90, 95% CI 0.74–1.10; $P < 0.001$ for noninferiority), and 1.11% per year in the dabigatran 150 mg group (RR 0.65, 95% CI 0.52–0.81; $P < 0.001$ for superiority) [31]. Major bleeding rates were 3.57% per year in the warfarin group, 2.87% per year in the dabigatran 110 mg group (RR 0.80, 95% CI 0.70–0.93; $P = 0.003$), and 3.32% per year in the dabigatran 150 mg group (RR 0.93, 95% CI 0.81–1.07; $P = 0.31$). The hemorrhagic stroke rate was 0.38% per year with warfarin, 0.12% per year with dabigatran at the 110 mg dose (RR 0.31, 95% CI 0.17–0.56; $P < 0.001$), and 0.10% per year with dabigatran at the 150 mg dose level (RR 0.26, 95% CI 0.14–0.49; $P < 0.001$) [30▪▪]. Mortality rates were 4.13% per year in the warfarin group, 3.75% per year with dabigatran 110 mg (RR 0.91, 95% CI 0.80–1.03; $P = 0.13$), and 3.64% per year with dabigatran 150 mg (RR 0.88, 95% CI 0.77–1.00; $P = 0.051$) [30▪▪,31].

A subgroup analysis included the secondary stroke prevention part of the RE-LY study exploring the treatment effects of dabigatran versus warfarin in patients who had a prior stroke or TIA [32]. Regarding stroke or systemic embolism, a finding consistent with that seen in the main RE-LY study was found in patients with prior stroke or TIA (RR 0.84, 95% CI 0.58–1.20 for dabigatran 110 mg versus warfarin; RR 0.75, CI 0.52–1.08 for dabigatran 150 mg versus warfarin). In this subgroup, there was also an 89 and 73% RR reduction in the incidence of hemorrhagic stroke in the dabigatran 110 mg and dabigatran 150 mg groups, respectively, compared with warfarin. With one exception (vascular death) all interaction *P* values were nonsignificant, indicating that the results in the subgroup of patients with TIA or stroke were comparable to those in the main study. In the RE-LY study, intracranial bleeding rates for all patients were lower in the dabigatran groups than in the warfarin group (110 mg b.i.d. dose: RR 0.30, 95% CI 0.19–0.45; 150 mg b.i.d. dose: RR 0.41, 95% CI 0.28–0.60; $P < 0.001$ superior to warfarin for both dabigatran doses) [30▪▪,31]. Intracranial bleeding rates were also lower in patients with prior stroke or TIA compared with warfarin ($P = 0.001$ for dabigatran 110 mg; $P = 0.007$ for dabigatran 150 mg) [32,33]. The bleeding risk was increased by the concomitant use of dabigatran and antiplatelet therapy [34], which also increased bleeding risk in patients on warfarin.

Dabigatran had a higher drop-out rate, due to gastrointestinal adverse events (e.g. dyspepsia) [30▪▪], and was associated with a small nonsignificant numerical increase in myocardial infarctions compared with warfarin [31]. In conclusion dabigatran is an important addition to the treatment options for stroke prevention in atrial fibrillation. Dabigatran was approved for use at the 150 mg b.i.d. dose in the USA [35], and for both doses in Europe.

Guideline recommendations on the use of dabigatran

The Canadian Cardiovascular Society 2010 guidelines recommend dabigatran 150 mg b.i.d. in preference to warfarin, with the 110 mg dose recommended for patients with decreased renal function, decreased body weight or at increased risk of major bleeding [36]. In the European Society of Cardiology (ESC) 2010 guidelines, dabigatran is considered an alternative to warfarin, with the 150 mg b.i.d. dose recommended for patients at low risk of bleeding (HAS-BLED score 0–2), and the 110 mg dose recommended for patients at high risk of bleeding (HAS-BLED score at least 3) [37]. The ESC 2010 guidelines also consider the 110 mg b.i.d. dose of dabigatran an option for patients with atrial fibrillation, and only one clinically relevant nonmajor stroke risk factor (heart failure, hypertension, diabetes, female sex, age 65–74, and vascular disease). The American College of Cardiology Foundation (ACCF)/American Heart Association Task Force (AHA)/Heart Rhythm Society (HRS) update to the ACC/AHA/ESC guidelines recommend the 150 mg b.i.d. dabigatran dose as an alternative to warfarin with a 75 mg dose recommended for patients with creatinine clearance of 15–30 ml/min [38]. The ACCF/AHA/HRS update also states that, because of the nonhemorrhagic side effects of dabigatran, patients with excellent INR control may have little benefit by switching from warfarin [38]. The update suggests that physicians consider the individual's ability to comply with b.i.d. dosing, availability of an INR management program, cost, patient preference, and other factors when choosing to treat with dabigatran or warfarin.

Another direct thrombin inhibitor in development is AZD0837. Phase II dose-ranging and tolerability studies of both extended release (150–450 mg once daily (o.d.) or 200 mg b.i.d.) and immediate release (150 mg b.i.d. or 350 mg b.i.d.) formulations have shown that the drug is generally well tolerated in patients with nonvalvular atrial fibrillation [39,40], although at the time of writing no plans for a phase III trial have been reported, and drug development has been suspended.

Oral direct factor Xa inhibitors

New oral direct factor Xa inhibitors under investigation for the prevention of stroke and systemic embolism in patients with atrial fibrillation are rivaroxaban, apixaban and edoxaban.

Rivaroxaban

Rivaroxaban (Xarelto) has been co-developed by Bayer Healthcare Pharmaceuticals and Johnson & Johnson Pharmaceutical Research & Development, L.L.C., and is administered in a fixed oral dose [41]. Rivaroxaban exhibits dose-dependent pharmacokinetics, and has a dual mode of elimination; one-third of the active drug is eliminated unchanged in the urine, and two-thirds is metabolized by the liver (of which half is excreted via the kidneys, and half excreted via the hepatobiliary route) [42]. The pharmacokinetics and pharmacodynamics of rivaroxaban are not influenced by sex or weight to the degree that any dose adjustment is required [43]. There is relevant interaction with strong inhibitors of both CYP3A4 and P-glycoprotein such as azole antimycotics or HIV protease inhibitors [44,45]. Pharmacokinetic and pharmacodynamic analyses have also indicated that although drug clearance is affected by renal function to some degree, rivaroxaban can be used effectively in patients with mild-to-moderate renal impairment (CrCl 30–79 ml/min) [46,47].

The prevention of stroke in patients with atrial fibrillation was investigated in the Rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism in atrial fibrillation (ROCKET-AF trial). In this phase III, double-blind, double-dummy, event-driven trial, the efficacy and safety of rivaroxaban (20 mg o.d. or 15 mg o.d. in patients with a CrCl 30–49 ml/min) was compared with warfarin in 14 264 patients in need of anticoagulation according to guidelines (i.e. $CHADS_2$ at least 2) [48▪▪]. ROCKET-AF, however, included patients with a much higher $CHADS_2$ score (mean 3.5) than RE-LY [30▪▪] or Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) [49▪▪] (means of around 2). The primary endpoint was stroke or systemic embolism. A total of 7131 patients were randomized to rivaroxaban and 7133 to warfarin. The rate of the primary endpoint in the per-protocol analysis was 1.7% per year for rivaroxaban compared with 2.2% per year for warfarin (HR 0.79, 95% CI 0.66–0.96; $P < 0.001$ for noninferiority). In the intention-to-treat population rivaroxaban was also noninferior to warfarin (2.1 versus 2.4% per year, HR 0.88, 95% CI 0.75–1.03; $P < 0.001$ for noninferiority; $P = 0.12$ for superiority) [48▪▪]. Principal safety endpoint rates (major and nonmajor clinically relevant bleeding) were similar in both groups (14.9 versus 14.5% per year; HR 1.03, 95% CI 0.96–1.11; $P = 0.44$ for superiority). Intracranial (0.5 versus 0.7% per year, HR 0.67, 95% CI 0.47–0.93; $P = 0.02$) and fatal bleeding (0.2 versus 0.5% per year, HR 0.50, 9% CI 0.31–0.79; $P = 0.003$) rates were lower with rivaroxaban. Adverse events were similar across groups. There was a small but significant increase in the number of epistaxis events in the rivaroxaban group (10.1 versus 8.6% in the warfarin group; $P < 0.05$).

The results from the subgroup analysis of patients with prior TIA or stroke were reported at the European Stroke Conference in May 2011. The subgroup comprised 7468 patients. Annual stroke rates were higher in patients with prior TIA or stroke compared with patients without cerebrovascular event (e.g. in the warfarin arm, 2.6% per year in those with prior TIA/stroke versus 1.7% per year in those without). The relative treatment effects of rivaroxaban versus warfarin were not statistically different between patients with and without prior TIA or stroke. More recently, the findings of another prespecified ROCKET-AF subgroup analysis were published, assessing the risks and benefits of the rivaroxaban 15 mg o.d. dose in the 2950 patients with moderate renal impairment (CrCl 30–49 ml/min) at enrolment [50]. Although patients with moderate renal impairment had higher rates of stroke, and bleeding than those without, regardless of treatment, the lower rivaroxaban dose yielded efficacy and safety results consistent with the overall ROCKET-AF trial.

Apixaban

Apixaban is manufactured by Bristol Myers-Squibb and Pfizer. In contrast to dabigatran and rivaroxaban, apixaban is eliminated approximately 25% renally, with 75% being eliminated through hepatobiliary elimination [51,52]. Clinical findings suggest that apixaban interacts with strong CYP3A4 inhibitors such as ketoconazole [53].

There are two studies investigating the prevention of stroke in patients with atrial fibrillation (Table 1). In the ARISTOTLE study, 18 201 patients with atrial fibrillation were treated with 5 mg oral doses of apixaban b.i.d. or warfarin [49▪▪,54]. The rate of primary outcome (stroke and systemic embolism) after a median 1.8 years of follow-up was 1.27% per year in the apixaban group, and 1.60% per year in the warfarin group, resulting in a HR of 0.79 with 95% CI 0.66–0.95 ($P = 0.01$ for superiority). The rate of major haemorrhage was 2.13% per year in the apixaban group compared with 3.09%

per year in the warfarin group (HR 0.69, 95% CI 0.60–0.80; $P < 0.001$). Mortality was reduced by 11% (HR 0.89, 95% CI 0.80–0.99; $P = 0.047$). Apixaban reduced the rate of haemorrhagic stroke (HR 0.51, 95% CI 0.35–0.75; $P < 0.001$), but did not significantly reduce the rate of ischemic, or uncertain type of stroke (HR 0.92, 95% CI 0.74–1.13; $P = 0.42$). The investigators also reported fewer discontinuations in the apixaban arm compared with warfarin (25.3 versus 27.5%, respectively; $P = 0.001$), with similar adverse event profiles observed.

The second study, Apixaban versus acetylsalicylic acid to prevent strokes, involved patients who had a contraindication to or were unwilling to take oral anticoagulants. The purpose of this study was to compare the effectiveness of apixaban with ASA in patients with atrial fibrillation considered unsuitable for warfarin [55▪▪]. The study was terminated prematurely by the Data and Safety Monitoring Board owing to the clear superiority of apixaban over ASA for the primary efficacy outcome (composite of stroke/systemic embolism). There were 51 primary outcome events (1.6% per year) among patients assigned to apixaban, and 113 (3.7% per year) in patients assigned to aspirin (HR 0.45; 95% CI 0.32–0.62; $P < 0.001$). There were 44 cases of major bleeding (1.4% per year) in the apixaban group, and 39 (1.2% per year) in the aspirin group (HR with apixaban, 1.13; 95% CI 0.74–1.75; $P = 0.57$), there were 11 cases of intracranial bleeding with apixaban, and 13 with aspirin (0.4% per year in both arms, HR 0.85, 95% CI 0.38–1.90; $P = 0.69$). In 764 patients with prior TIA or stroke there were 10 primary outcome events in those randomized to apixaban (2.5% per year), and 33 in those randomized to aspirin (8.3% per year), showing that the treatment effects for apixaban compared with aspirin were comparable between patients with atrial fibrillation with and without prior TIA or stroke.

Edoxaban

Edoxaban (DU-176b) is manufactured by Daiichi Sankyo. Phase I data for this substance have been published [56,57], as well as the findings of a phase II dose-finding study in patients with atrial fibrillation [58]. This study showed edoxaban 30 mg q.d. (daily) and 60 mg q.d. dose regimens to have a safety profile similar to warfarin, although those treated with the edoxaban 30 mg b.i.d. or 60 mg b.i.d. regimens had more bleeding events versus warfarin. Based on the findings of these trials, the effective anticoagulation with factor XA next generation in atrial fibrillation-thrombolysis in myocardial infarction study 48 global phase III safety/efficacy study on stroke prevention in patients with atrial fibrillation was initiated [59] (Table 1). In this 24-month trial, edoxaban o.d. (30 mg or 60 mg) is investigated versus warfarin, with more than 21 000 patients enrolled.

CONCLUSION

After 60 years of using oral vitamin K antagonists, the time has come for new substances. At present it is difficult to conclude which of the new drugs has the highest efficacy and the best benefit–risk ratio. There are no head-to-head comparisons (and there will most likely never be such studies), and the trials investigated different populations. Calculated numbers-needed-to-treat (NNT) give some hint: NNT are 625 for dabigatran low dose, 172 for dabigatran high dose, 303 for apixaban and 200 for rivaroxaban, all versus warfarin. The high dose of dabigatran has the highest benefit for preventing stroke (including ischemic stroke), whereas apixaban shows advantages in reducing the risk of bleeding complications and has been investigated in comparison with ASA. Rivaroxaban seems to be best suited for patients with high stroke risk.

Both oral direct thrombin antagonists and factor Xa inhibitors have advantages over warfarin and other VKAs in a number of ways:

(1) New anticoagulants are administered in a fixed dose irrespective of sex, weight and age [for apixaban there is the recommendation to go for 2.5 mg b.i.d. if weight is 60 kg or less (and age is at least 80 years)].
(2) There are no interactions with food and few interactions with drugs.
(3) There is no need to monitor INR values or other coagulation parameters. This may be a particular advantage for patients who have had a disabling stroke, and find it difficult to attend coagulation clinics.
(4) Studies conducted up to this point suggest that the new oral anticoagulants are superior to VKAs.
(5) The incidences of bleeding complications are comparable to, and in the case of intracranial bleeds, are lower than those associated with oral VKAs.
(6) In patients with prior TIA or stroke the new anticoagulants are as effective as in patients without prior TIA or stroke. As the secondary stroke rate is higher after TIA or stroke, the absolute benefit is higher.
(7) All studies up to now excluded patients in the acute phase of stroke. There is, however, no reason to delay the treatment in patients with

mild to moderate strokes beyond 3–6 days after the acute event. Patients with TIA can be treated within 24 h after imaging to exclude cerebral bleed.

Due to the quick onset and offset of action of the new anticoagulants, compliance and adherence is much more important than with VKAs. Education for both physicians and patients on this issue is of paramount importance.

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Conflicts of interest

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- ■ of special interest
- ■■ of outstanding interest

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