

Review of atrial fibrillation outcome trials of oral anticoagulant and antiplatelet agents

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Atrial fibrillation (AF) is strongly associated with cardioembolic stroke, and thromboprophylaxis is an established means of reducing stroke risk in patients with AF. Oral vitamin K antagonists such as warfarin have been the mainstay of therapy for stroke prevention in patients with AF. However, they are associated with a number of limitations, including excessive bleeding when not adequately controlled. Antiplatelet agents do not match vitamin K antagonists in terms of their preventive efficacy. Dual-antiplatelet therapy (clopidogrel and acetylsalicylic acid) or combined antiplatelet–vitamin K antagonist therapy in AF has also failed to provide convincing evidence of their additional benefit over vitamin K antagonists alone. Novel oral anticoagulants, including the direct thrombin inhibitor dabigatran and direct Factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban, have now been approved or are currently in late-stage clinical development in AF. These newer agents may provide a breakthrough in the optimal management of stroke risk.

Keywords Anticoagulants • Apixaban • Aspirin • Atrial fibrillation • Clopidogrel • Dabigatran • Drug discovery • Rivaroxaban • Stroke • Warfarin

Introduction

Previous estimates have suggested that atrial fibrillation (AF) affects over 2 million people in the USA and over 4 million across the European Union.^{1,2} Atrial fibrillation is more common in older people,¹ suggesting that it will become an ever-greater problem in an increasingly ageing population.

Patients with AF are reported to have a five-fold increased risk of stroke; moreover, compared with the other identified risk factors for stroke (hypertension, heart failure, and coronary heart disease), AF has the strongest association.³ Atrial fibrillation-related stroke is cardiac in origin; thrombi form in the left atrial appendage and embolize, causing ischaemic stroke.² Therefore, antithrombotic therapy has become an established method of preventing stroke in patients with AF.

This article reviews the current role of antithrombotic therapy in patients with non-valvular AF, and examines the relative clinical benefit of current oral anticoagulant and antiplatelet therapies. The latest developments in clinical trials of novel oral anticoagulants are also reviewed.

Assessing the level of stroke risk in atrial fibrillation: risk stratification

Numerous risk stratification schemes have been developed to help predict the level of stroke risk in patients with AF (low, moderate, or high) and to manage them accordingly. Among the best known is the CHADS₂ scale, where points are attributed to the presence of known risk factors: congestive heart failure, hypertension, age ≥ 75 years, diabetes (1 point each), or previous stroke/transient ischaemic attack (TIA; two points, to reflect its greater associated risk).⁴ Stratification schemes (and management guidelines) have also been developed by the joint Task Force of the American College of Cardiology, American Heart Association, and European Society of Cardiology (ACC/AHA/ESC),² and by the American College of Chest Physicians (ACCP).⁵ Because the various schemes have been developed by independent groups over several years, there is some heterogeneity between them; this leads to considerable differences in a patient's predicted level of stroke risk, depending on the scheme used. An analysis of 12 published risk stratification schemes showed that, in a representative

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sample of 1000 patients with AF, the proportion of those classified as 'low risk' varied from 7% to 42%, depending on the scheme used.⁴ A similar analysis by Lip *et al.*⁶ found that, of a sample of patients with AF from the Euro Heart Survey ($n = 1084$), the percentage defined as 'low risk' ranged from 9% to 48% across several different schemes. Interestingly, the 9% relates to the 'Birmingham 2009' scheme, an adaptation of CHADS₂ referred to as CHA₂DS₂-VASc, which incorporates additional risk factors including vascular disease, age 65–74 years, and female gender. In the CHA₂DS₂-VASc scoring scheme, age ≥ 75 years is also assigned a greater weight, i.e. two points.⁶ In this 9% of patients, the incidence of thromboembolism was 0% (compared with 1.4% using the CHADS₂ definition), suggesting that they were 'truly' low risk.⁶ Taken together, these analyses indicate that perhaps as many as 90% of patients with AF can be classed as being at moderate-to-high risk of stroke. A recent retrospective analysis of 73 538 patients with AF in Denmark assessed the predictive capability of the new scheme and found the rate of thromboembolism per 100 person-years in patients with a zero score was 1.67 [95% confidence interval (CI) 1.47–1.89] for CHADS₂ and 0.78 (95% CI 0.58–1.04) for CHA₂DS₂-VASc at 1 year.⁷ In all risk categories except for CHA₂DS₂-VASc score equal to 0 there was a reduction in risk with vitamin K antagonist (VKA) treatment. Another study followed 79 844 patients with AF in the UK General Practice Research Database for an average of 4 years.⁸ In this study, the annual stroke rate per 100 person-years in patients with a zero score was 1% for CHADS₂ and 0.5% for CHA₂DS₂-VASc. Interestingly, a small-scale Chinese study also reported that, unlike CHADS₂, the CHA₂DS₂-VASc score was an independent predictor of left atrial thrombus in patients with paroxysmal AF.⁹ However, larger studies are needed to validate this. Notably, the most recent ESC guidelines incorporate CHA₂DS₂-VASc, recommending that CHADS₂ be used for initial assessments of the need for oral anticoagulation, with CHA₂DS₂-VASc being invoked for further refinement in patients with a CHADS₂ score of 0–1.¹⁰

Thromboprophylaxis with antithrombotic agents is associated with an increased risk of bleeding, and guidelines recommend that individual patients' bleeding risks should also be considered before starting antithrombotic treatment.^{2,10–12} Because many of the risk factors for stroke and bleeding are similar, the rate of major haemorrhage is higher in patients with higher CHADS₂ scores,^{6,13,14} and so an accurate tool for assessing individual bleeding risk is of value to help guide treatment. A comparison of bleeding risk schemes using a trial cohort of 7329 patients with AF found the HAS-BLED scheme to have the best predictive value.¹⁴ The risk factors included in the HAS-BLED scheme (given 1 point each) are hypertension, abnormal renal or liver function, history of stroke, history of bleeding or bleeding predisposition, labile international normalized ratios (INRs), age > 65 years, and concomitant drug use or alcohol abuse. The predictive ability of the HAS-BLED scheme has also been compared with the alternative scheme, HEMORR₂HAGES, in a Danish registry of 118 584 patients with AF.¹⁵ HEMORR₂HAGES, like HAS-BLED, is a point scheme with two points assigned for a prior bleed and one point for other risk factors including: hepatic or renal disease, ethanol abuse, malignancy, older (age > 75 years), reduced platelet count or function, hypertension (uncontrolled), anaemia, genetic factors, excessive fall risk, and

stroke.¹⁶ The two schemes had a similar ability to predict the rate of hospitalization or death from major bleeding in 1 year, with both schemes demonstrating increasing bleeding rates with increasing score.¹⁵ The authors concluded, however, that the simplicity of HAS-BLED was advantageous as it could be used more easily in clinical practice. The Canadian Cardiovascular Society (CCS) and ESC 2010 guidelines both advocate the use of the HAS-BLED scheme, with HAS-BLED score ≥ 3 deemed to indicate high risk of bleeding, and caution and regular review recommended regardless of whether the patient is treated with an oral anticoagulant or acetylsalicylic acid (ASA).^{10,12}

Oral anticoagulant therapy: vitamin K antagonists

Until recently, VKAs such as warfarin were the only approved means of oral anticoagulant therapy for stroke prevention in AF. According to ACC/AHA/ESC 2006/2011 and ACCP 2008 guidelines, patients with moderate-to-high risk of stroke should be considered for stroke prophylaxis with a VKA.^{2,5,11} The ESC 2010 guidelines recommend that patients with a CHADS₂ score ≥ 2 should receive oral anticoagulation therapy; patients with a CHADS₂ score of < 2 should be assessed using CHA₂DS₂-VASc.¹⁰ Those with a CHA₂DS₂-VASc score of 1 may receive either oral anticoagulation therapy or ASA (with oral anticoagulation the preferred option of the two), and patients with a CHA₂DS₂-VASc score of 0 may receive either ASA or no antithrombotic therapy—with the guidelines also stating that no antithrombotic therapy is the preferred choice in these patients.¹⁰

In 2007, Hart *et al.*¹⁷ published the findings of a comprehensive meta-analysis of data from 29 randomized clinical trials assessing the efficacy and safety of antithrombotic agents (including VKAs) in patients with non-valvular AF. Reviewing six trials that compared a VKA with placebo or control, the meta-analysis found that adjusted-dose warfarin reduced the relative risk (RR) of stroke by 64% (95% CI 49–74) vs. placebo or control (53 events in 2396 patient-years vs. 133 events in 2207 patient-years) (Figure 1A). When ischaemic stroke alone was analysed, the RR reduction with adjusted-dose warfarin was 67% (95% CI 54–77).¹⁷ Compared with placebo or control, a 26% (95% CI 3–43) reduction in all-cause mortality was also seen with adjusted-dose warfarin (110 vs. 143 deaths).

Vitamin K antagonist therapy has considerable limitations, one of which is its association with increased bleeding. The 2007 meta-analysis showed that dose-adjusted warfarin increased the RR of intracranial haemorrhage by 128% compared with ASA; the difference in absolute risk between warfarin and ASA was small (0.2% per year), but was reported as being statistically significant.¹⁷ It has been suggested that rates of haemorrhage in younger non-inception trial cohorts underestimate warfarin-related bleeding in practice.¹³ In a cohort of patients with AF receiving warfarin who were ≥ 65 years of age, the rate of intracranial haemorrhage was 2.5%.¹³ The first 90 days of warfarin, age ≥ 80 years, and INR ≥ 4.0 were associated with an increased risk of major haemorrhage. Warfarin use was the cause of 15% of the drug-related adverse events in a cohort of 1247 long-term care residents.¹⁸ In

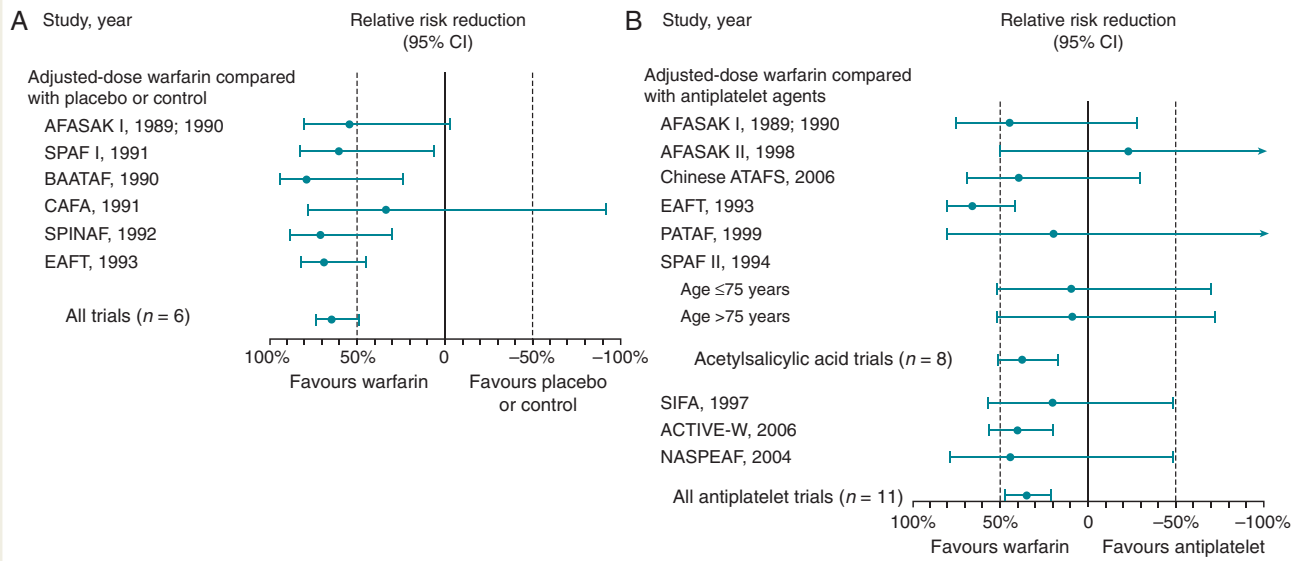


Figure 1 Relative effects of antithrombotic therapies on all stroke from randomized trials in patients with atrial fibrillation: (A) adjusted-dose warfarin compared with placebo or no treatment, (B) adjusted-dose warfarin compared with antiplatelet agents. Details of the analyses conducted are described in the original publication by Hart *et al.*¹⁷ Figures reproduced with permission from *Annals of Internal Medicine*.

fact, 17% of first admissions for intracranial haemorrhage have been found to be associated with anticoagulation therapy, with 98% of these patients receiving warfarin treatment.¹⁹

Vitamin K antagonists also have a delayed onset of action; in the first few days, heparin bridging therapy is required until the anticoagulant effect of the VKA is established.²⁰ Vitamin K antagonists are also associated with variable dose–response profiles: reasons for this include environmental and hereditary factors (body weight, age, and genetic polymorphisms), and interactions with foods and drugs.²⁰ The narrow therapeutic window of VKAs (INR of prothrombin times ranging between 2.0 and 3.0 in patients with AF)²⁰ is another limitation. Patients receiving VKA therapy, therefore, need regular coagulation monitoring and dose adjustment.

Thus, VKAs are often underused in the clinical setting. For example, a retrospective US cohort study of hospitalized patients with AF ($n = 945$) found that, although 86% of patients were classed as being at high risk of stroke, only 55% were given a VKA.²¹ More surprisingly, 21% of high-risk patients did not receive a VKA or ASA. There are similar findings regarding the suboptimal use of VKAs in those at high risk of stroke in the out-of-hospital setting.²²

Antiplatelet therapy

Acetylsalicylic acid has been widely used as an agent for stroke prophylaxis in patients with AF. Until recently, guidelines recommended ASA therapy only in patients with non-valvular AF who are considered at low risk of stroke, or in whom VKA therapy is contraindicated.^{2,5} However, the ESC 2010 guidelines and the ACC Foundation/AHA/Heart Rhythm Society (ACCF/AHA/HRS) focussed update to the ACC/AHA/ESC 2006 guidelines include a role for clopidogrel use in conjunction with ASA,

suggesting that this dual-antiplatelet combination could be considered for stroke prevention in patients for whom oral anticoagulation therapy may be unsuitable.^{10,23}

A number of studies have evaluated the efficacy of antiplatelet agents, principally ASA, in reducing thromboembolism in patients with AF. In their meta-analysis, Hart *et al.*¹⁷ reported a 19% (95% CI –1 to 35) reduction in the RR of stroke in patients with AF treated with ASA compared with placebo or no treatment (179 events in 3432 patient-years vs. 209 events in 3302 patient-years). However, this reduction in risk was not statistically significant. Furthermore, the dose of ASA varied widely from 50 to 1300 mg per day in the studies included in the meta-analysis with most of the beneficial effects of ASA driven from the Stroke Prevention in Atrial Fibrillation (SPAF) I study, which utilized a 325 mg dose.^{10,24} In contrast, the Japan Atrial Fibrillation Stroke Trial compared an ASA dose of 150–200 mg per day with no treatment in 871 patients with AF.²⁵ This trial was stopped early due to a non-significant increase in the risk of major bleeding of 1.6% with ASA, compared with 0.4% in the no-treatment group. Also, the greater number of primary endpoint events (cardiovascular death, symptomatic brain infarction, or TIA) in the ASA arm (3.1% per year) compared with no-treatment group (2.4% per year) meant that treatment with ASA was unlikely to be superior to no treatment.

A comparison of antiplatelets (including clopidogrel, triflusal, and indobufen as well as ASA) with VKA therapy in the meta-analysis by Hart *et al.* revealed that adjusted-dose warfarin reduced the RR of all stroke by 37% (95% CI 23–48) compared with antiplatelet therapy (180 vs. 282 events in 8946 patient-years) (Figure 1B).¹⁷ The modest effect of antiplatelet agents on stroke risk may be more due to the inhibition of platelet thrombi in the carotid and cerebral arteries than the inhibition of cardiogenic

Table 1 Studies of dual-antiplatelet therapy (ASA and clopidogrel) in patients with non-valvular atrial fibrillation

Study	Population	Treatment groups	Primary efficacy endpoint	Major bleeding endpoint	Annual risk	Relative risk (95% CI) + P value
ACTIVE W (2006) ²⁷	AF pts (n = 6706) with (≥ 1 of): age ≥ 75 yrs; hypertension; previous stroke, TIA, or non-CNS SE; LVEF < 45%; PAD or: age 55–74 yrs with diabetes or previous CAD	(1) VKA (INR 2–3) or (2) ASA (75–100 mg/day) + clopidogrel (75 mg/day)	Stroke, non-CNS SE, MI, or vascular death	Transfusion ≥ 2 units of red blood cells or equivalent of whole blood, or severe bleeding (eg. associated with death, Hb drop ≥ 5 g/dL)	Primary events: 5.60% (ASA + clopi) vs. 3.93% (VKA) Major bleeding: 2.42% (ASA + clopi) vs. 2.21% (VKA) Net clinical benefit (primary endpoint, major bleed, and death): 8.32% (ASA + clopi) vs. 6.45% (VKA)	1.44 (1.18–1.76), P = 0.0003 1.10 (0.83–1.45), P = 0.53 1.31 (1.12–1.54), P = 0.0008
ACTIVE A (2009) ²⁸	See ACTIVE W; pts (n = 7554) considered unsuitable for VKA therapy	ASA (75–100 mg/day) plus (1) clopidogrel (75 mg/day) or (2) placebo	See ACTIVE W	See ACTIVE W	Primary events: 6.8% (ASA + clopi) vs. 7.6% (ASA) Major bleeding: 2.0% (ASA + clopi) vs. 1.3% (ASA)	0.89 (0.81–0.98), P = 0.01 1.57 (1.29–1.92), P < 0.001

ACTIVE, Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; AF, atrial fibrillation; ASA, acetylsalicylic acid; CAD, coronary artery disease; CI, confidence interval; clopi, clopidogrel; CNS, central nervous system; g/dL, grams per decilitre; Hb, haemoglobin; INR, international normalized ratio; LVEF, left ventricular ejection fraction; mg/day, milligrams per day; MI, myocardial infarction; PAD, peripheral arterial disease; pts, patients; RR, relative risk; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist; yrs, years.

thrombi that occur in AF.²⁶ However, it is likely that the lower bleeding risk with antiplatelet agents compared with that of VKAs (albeit at the cost of reduced efficacy) remains their key attraction.

Are combination therapies a viable alternative to vitamin K antagonist or antiplatelet monotherapy in atrial fibrillation?

Dual-antiplatelet therapy

In previous years, the relative efficacy and safety profiles of dual-antiplatelet therapy (ASA and clopidogrel) have been assessed in patients with AF (Table 1). In the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) W study, patients with electrocardiogram-confirmed AF and at least one risk factor for stroke were randomized to receive clopidogrel with ASA or VKA therapy (target INR 2.0–3.0).²⁷ Clopidogrel plus ASA therapy was associated with significantly more major vascular events [stroke, non-central nervous system (CNS) systemic embolism, myocardial infarction, or vascular death] than VKA therapy ($P = 0.0003$) (Table 1). Rates of major bleeding were similar between the two groups, but there were significantly more cases of minor bleeding in the clopidogrel plus ASA group ($P = 0.0009$). The study was stopped early owing to the clear superiority of VKA therapy.

Acetylsalicylic acid is prescribed in patients with AF who cannot (or will not) tolerate VKAs.²⁸ The ACTIVE A trial compared the efficacy and safety of clopidogrel plus ASA vs. placebo plus ASA in patients with AF who were at increased risk of stroke, but who were considered unsuitable for VKA therapy (Table 1).²⁸ In the clopidogrel plus ASA group, there were significantly fewer major vascular events compared with the placebo plus ASA group ($P = 0.01$) (Table 1). This effect on the primary endpoint was mainly due to the reduced incidence of stroke. However, major bleeding occurred more frequently in patients taking clopidogrel than those receiving placebo ($P < 0.001$), with the most common site of bleeding being the gastrointestinal tract. Clopidogrel plus ASA increased the risk of major extracranial bleeding by 51% and the risk of major intracranial bleeding by 87%. There was no significant difference in net clinical benefit (major vascular events plus major bleeding) between the two groups.

Antiplatelet plus vitamin K antagonist therapy

Studies combining VKAs with antiplatelet therapy in patients with AF have also been conducted. Their main aim was to assess whether combination therapy enabled the intensity of anticoagulation to be reduced, lessening the likelihood of excessive bleeding and the need for regular monitoring, while maintaining protective efficacy (Table 2).

The SPAF III trial compared ASA and fixed-dose warfarin (to maintain INR 1.2–1.5) with adjusted-dose warfarin alone (target INR 2.0–3.0) in patients with non-valvular AF at high risk of thromboembolism.²⁹ The trial was stopped early, owing to a

Table 2 Studies of combined oral anticoagulant and antiplatelet therapy in patients with atrial fibrillation

Study	Population	Treatment groups	Primary efficacy endpoint	Major/severe bleeding endpoint	Key findings	P value (if given)
SPAF III ²⁹	Pts (<i>n</i> = 1044) with NVAF and (≥ 1 of): LV dysfunction or CHF; hypertension; ischaemic stroke, TIA, or SE; female; and age > 75 yrs	(1) ASA 325 mg/day + low-dose warfarin (INR 1.2–1.5) (2) Adjusted-dose warfarin (INR 2–3)	Ischaemic stroke, SE	Fatal, life-threatening or potentially life-threatening, bleeding that leads to reoperation, or moderate or severe blood loss ³⁰	Primary events (annual rate): 7.9% (low-dose warf + ASA) vs. 1.9% (adjusted-dose warf) Major bleeding (annual rate): 2.4% (low-dose warf + ASA) vs. 2.1% (adjusted-dose warf)	<i>P</i> < 0.0001 NS
AFASAK 2 ³¹	Pts (<i>n</i> = 677) with NVAF, ≥ 18 yrs	(1) Warfarin (1.25 mg/day) (2) Warfarin (1.25 mg/day) + ASA (300 mg/day) (3) ASA (300 mg/day) (4) Adjusted-dose warfarin (INR 2–3)	All stroke, SE	Fatal, life-threatening or potentially life-threatening, requiring surgery or blood transfusion	Primary events (after 1 yr): 5.8% (low-dose warf), 7.2% (low-dose warf + ASA), 3.6% (ASA), 2.8% (adjusted-dose warf) Major bleeding events: 3 (low-dose warf), 1 (warf + ASA), 5 (ASA), 4 (adjusted-dose warf)	<i>P</i> = 0.67
Edvardsson <i>et al.</i> ³²	Pts (<i>n</i> = 668) with NVAF and no prior stroke/TIA	(1) Warfarin (1.25 mg/day) + ASA (75 mg/day) (2) No treatment (control)	All stroke	Bleeding warranting exclusion from the trial (protocol-specified)	All stroke: 9.6% (warf + ASA) vs. 12.3% (control) Reported bleeds: 5.7% (warf + ASA) vs. 1.2% (control)	HR 0.78 (95% CI 0.49–1.23), <i>P</i> = 0.28 HR 5.11 (95% CI 1.75–15.0), <i>P</i> = 0.003
FFAACs ³³	Pts with NVAF and: (1) history of TE or (2) age > 65 yrs plus 1 of: hypertension, CHF, or LV dysfunction	Adjusted-dose fluindione (INR 2–2.6) plus (1) ASA (100 mg/day) or (2) Placebo	Stroke, SE, MI, or vascular death	Requiring specific treatment (e.g. transfusion) or hospitalization	Primary events (per 100 pt-yrs): 7.93 (fluin + ASA) vs. 2.87 (fluin) Severe bleeds (events per 100 pt-yrs): 4.8 (fluin + ASA) vs. 1.4 (fluin)	<i>P</i> = 0.21 <i>P</i> = 0.35
NASPEAF ³⁴	<i>n</i> = 1209 High risk: (1) Pts with NVAF + prior embolism and (2) pts with mitral stenosis with/without prior embolism All others: intermediate risk	Intermediate risk: (1) Triflusal (600 mg/day); (2) VKA (INR 2–3); and (3) Triflusal (600 mg/day) + VKA (INR 1.25–2) High risk: (1) VKA (INR 2–3) and (2) Triflusal (600 mg/day) + VKA (INR 1.4–2.4)	Stroke, TIA, SE, or vascular death	Severe: requiring hospital admission, blood transfusion, or surgery	Intermediate risk (events per 100 pt-yrs): Primary: 3.82 (trifl), 2.70 (VKA), 0.92 (combined) Severe bleeding: 0.35 (trifl), 1.80 (VKA), 0.92 (combined) Net benefit (primary outcome and severe bleeding): 3.82 (trifl), 3.78 (VKA), 1.48 (combined) High risk (events per 100 pt-yrs): Primary: 4.76 (VKA) vs. 2.44 (combined) Severe bleeding: 2.13 (VKA) vs. 2.09 (combined) Net benefit: 5.58 (VKA) vs. 3.84 (combined)	<i>P</i> < 0.05 (combined vs. others) NS <i>P</i> < 0.05 (combined vs. others) <i>P</i> < 0.05 NS NS
NASPEAF follow-up ³⁵	Pts (<i>n</i> = 400) from NASPEAF 2004 study ³⁴ + new pts (<i>n</i> = 174)	(1) VKA (INR 2–3) (2) VKA (INR 1.9–2.5) + triflusal (600 mg/day) (3) VKA (INR 1.9–2.5) + triflusal (300 mg/day) (4) VKA (INR 1.9–2.5) + ASA (100 mg/day)	Stroke, SE, ACS, sudden death, death ≤ 30 days after an event or severe bleeding	See NASPEAF 2004 definition	Primary events (per 100 pt-yrs): 2.86 (VKA), 1.36 (VKA + trifl 600 mg/day), 2.67 (VKA + trifl 300 mg/day), 2.83 (VKA + ASA) Severe bleeding (events per 100 pt-yrs): 2.47 (VKA), 1.51 (VKA + trifl 600 mg/day), 1.33 (VKA + trifl 300 mg/day), 6.6 (VKA + ASA)	<i>P</i> = 0.039 (VKA + trifl 600 mg/day vs. VKA) <i>P</i> = 0.008 (VKA + ASA vs. all others)

Flaker et al. ³⁶	SPORTIF post-hoc analysis	(1) Warfarin (INR 2–3) (2) Warfarin (INR 2–3) + ASA (≤100 mg/day) (3) Ximelagatran (36 mg bid) (4) Ximelagatran (36 mg bid) + ASA (≤100 mg/day)	Stroke, SE	Fatal, involved a critical anatomical site, or Hb drop ≥2 g/dL or ≥2 units of blood transfused	Primary events (annual rate): 1.55% (warf) vs. 1.7% (warf + ASA) 1.4% (ximel) vs. 1.7% (ximel + ASA) Major bleeding events (annual rate): 2.3% (warf) vs. 3.9% (warf + ASA) 1.9% (ximel) vs. 2.0% (ximel + ASA)	P = 0.78 P = 0.52 P = 0.01 P = 0.83
	SPORTIF post-hoc analysis	(1) Warfarin (INR 2–3) (2) Warfarin (INR 2–3) + ASA (≤100 mg/day) (3) Ximelagatran (36 mg bid) (4) Ximelagatran (36 mg bid) + ASA (≤100 mg/day)	Stroke, SE	Fatal, involved a critical anatomical site, or Hb drop ≥2 g/dL or ≥2 units of blood transfused	Primary events (annual rate): 1.55% (warf) vs. 1.7% (warf + ASA) 1.4% (ximel) vs. 1.7% (ximel + ASA) Major bleeding events (annual rate): 2.3% (warf) vs. 3.9% (warf + ASA) 1.9% (ximel) vs. 2.0% (ximel + ASA)	P = 0.78 P = 0.52 P = 0.01 P = 0.83

ACS, acute coronary syndrome; AFASAK, Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation study; ASA, acetylsalicylic acid; bid, twice daily; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; FFAACS, Fluidione, Fibrillation Auriculaire, Aspirin et Contraste Spontané; fluin, fluidione; g/dL, grams per decilitre; Hb, haemoglobin; HR, hazard ratio; INR, international normalized ratio; LV, left ventricular; mg/day, milligrams per day; MI, myocardial infarction; NASPEAF, National Study for Prevention of Embolism in Atrial Fibrillation; NS, not significant; NVAF, non-valvular atrial fibrillation; pts, patients; SE, systemic embolism; SPAF, Stroke Prevention in Atrial Fibrillation; SPORTIF, Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation; TE, thromboembolism; TIA, transient ischaemic attack; trifl, triflusal; VKA, vitamin K antagonist; warf, warfarin; ximel, ximelagatran; yrs, years.

significantly higher rate of ischaemic stroke and systemic embolism in the combination group compared with warfarin alone ($P < 0.0001$). There was no difference in major bleeding rates between the groups. The Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK 2) study, assessing the efficacy and safety of fixed, low-dose warfarin with (or without) ASA compared with ASA or adjusted-dose warfarin (INR 2.0–3.0) alone, was also stopped early in light of the SPAF III findings.³¹ No significant difference in the cumulative rate of primary events (stroke or systemic thromboembolic event) between the different treatment groups was reported after 1, 2, or 3 years ($P = 0.67$; Table 2). A higher cumulative rate of bleeding was seen with warfarin after 3 years ($P = 0.003$). The investigators in both trials concluded that the very low intensity of anticoagulation achieved with the combination therapy did not justify replacing the current adjusted-dose VKA therapy.^{29,31} A later study compared low-dose warfarin plus ASA with no treatment in patients with AF who were not recommended anticoagulation therapy (described as 'low-to-medium risk').³² They also reported that combination therapy did not significantly reduce stroke risk, but was associated with higher bleeding rates (Table 2). However, the results may also have been affected by the lower than planned number of eligible patients included.

Other studies such as Fluidione, Fibrillation Auriculaire, Aspirin et Contraste Spontané (FFAACS), and National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) have also assessed the efficacy and safety of combination therapy using higher-intensity anticoagulation than above (Table 2).^{33–36} However, their overall findings are inconclusive; some report a positive effect of combined therapy compared with VKA monotherapy on the different endpoints, while others report no difference or a negative effect (Table 2).

In summary, the efficacies of clopidogrel plus ASA or antiplatelet plus VKA therapies in such trials do not provide strong evidence that they should replace VKA monotherapy in patients with non-valvular AF. Future studies with newer antiplatelet agents such as prasugrel and ticagrelor might force a reassessment; however, this is purely speculative.

New oral anticoagulants in development

Given the inherent limitations of VKA therapy, and the lack of a suitable alternative dual-antiplatelet or combined antiplatelet—VKA strategy, attention has switched to developing new oral anticoagulants. Rather than acting on several different factors in the coagulation cascade, as VKAs do, new oral anticoagulants are designed to target a specific component of the cascade. Oral agents with little potential for food or drug interactions, and which can be administered in fixed doses without routine coagulation monitoring, have the potential to simplify long-term anticoagulant therapy.

There are currently many novel oral anticoagulants that have recently been approved or are in the advanced stages of clinical research in the AF setting. Here, those agents with completed or ongoing phase II and III trials in patients with AF are discussed.

Table 3 Summary of key phase III completed or ongoing trials with novel oral anticoagulants

Study	Population	Treatment groups	Primary efficacy and safety endpoints	Key findings
RE-LY ^{37,38} Randomized, open-label, parallel-group, multicentre non-inferiority trial	Pts (<i>n</i> = 18 113) with NVAf and ≥1 of: Prior stroke/TIA, age ≥75 yrs, symptomatic heart failure (NYHA class ≥2), LVEF < 40%; or age 65–74 yrs + diabetes mellitus, hypertension, or CAD	(1) Dabigatran etexilate 110 mg bid (blinded) (2) Dabigatran etexilate 150 mg bid (blinded) (3) Open-label warfarin (INR 2–3)	Primary efficacy endpoint: composite of stroke and SE Primary safety outcome: major bleeding (Hb drop ≥2 g/dL, transfusion ≥2 units of blood, bleeding in critical area or organ, life-threatening bleeding)	Primary efficacy endpoint: 110 mg bid vs. warf: RR 0.90 (95% CI: 0.74–1.10); <i>P</i> (superiority) = 0.30 150 mg bid vs. warf: RR 0.65 (95% CI: 0.52–0.81); <i>P</i> (superiority) < 0.001 Primary safety outcome: 110 mg bid vs. warf: RR 0.80 (95% CI: 0.70–0.93); <i>P</i> (superiority) = 0.003 150 mg bid vs. warf: RR 0.93 (95% CI: 0.81–1.07); <i>P</i> (superiority) = 0.32
ROCKET AF ^{39,40} Randomized, double-blind, double-dummy, parallel-group, multicentre non-inferiority trial	Pts (<i>n</i> = 14 264) with NVAf and prior stroke/TIA or SE, or ≥2 of: CHF or LVEF ≤35%, hypertension, age ≥75 yrs, diabetes mellitus ^a	(1) Double-blind rivaroxaban 20 mg od (15 mg od for pts with creatinine clearance 30–49 mL/min) (2) Double-blind warfarin (INR 2–3)	Primary efficacy endpoint: composite of stroke and SE Primary safety outcome: major and non-major clinically relevant bleeding (major: clinically overt bleeding associated with fatal outcome, involving a critical site, Hb drop ≥2 g/dL, transfusion ≥2 units of packed RBCs or whole blood)	Primary efficacy endpoint: Per protocol population, on treatment: rivaroxaban vs. warf: HR 0.79 (95% CI: 0.66–0.96); <i>P</i> (non-inferiority) < 0.001 Safety population, on treatment: rivaroxaban vs. warf: HR 0.79 (95% CI: 0.65–0.95); <i>P</i> (superiority) = 0.02 Intention-to-treat: rivaroxaban vs. warf: HR 0.88 (95% CI: 0.74–1.03); <i>P</i> (non-inferiority) < 0.001 Primary safety outcome: rivaroxaban vs. warf: HR 1.03 (95% CI: 0.96–1.11) <i>P</i> (superiority) = 0.44
ARISTOTLE ^{41,42} Randomized, double blind, double-dummy, active (warfarin) controlled non-inferiority trial	Pts (<i>n</i> = 18 201) with NVAf and ≥1 of: Prior stroke/TIA or SE, age ≥75 yrs, symptomatic CHF or LVEF ≤40%, diabetes mellitus, hypertension	(1) Double-blind apixaban 5 mg bid (2.5 mg bid for pts with ≥2 of the following at baseline: age ≥80 yrs, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL) (2) Double-blind warfarin (INR 2–3)	Primary efficacy endpoint: composite of stroke and SE Primary safety outcome: major bleeding (clinically overt bleeding plus ≥1 of: Hb drop ≥2 g/dL; transfusion of ≥2 units of packed RBCs; fatal bleeding or bleeding that occurs in ≥1 critical site)	Primary efficacy endpoint: apixaban vs. warf: HR 0.79 (95% CI: 0.66–0.95); <i>P</i> (superiority) = 0.01 Primary safety outcome: apixaban vs. warf: HR 0.69 (95% CI: 0.60–0.80); <i>P</i> < 0.001
AVERROES ^{43,44} Randomized, double-blind, double-dummy superiority trial	Pts (<i>n</i> = 5599) aged ≥50 yrs with NVAf unsuitable for VKA use and ≥1 of: Prior stroke/TIA, age ≥75 yrs, heart failure (NYHA class ≥2), or LVEF ≤35%, diabetes mellitus, hypertension, PAD	(1) Double-blind apixaban 5 mg bid (or 2.5 mg bid – see ARISTOTLE) (2) Double-blind ASA (81–324 mg/day)	See ARISTOTLE	Primary efficacy endpoint: apixaban vs. ASA: HR 0.45 (95% CI: 0.32–0.62); <i>P</i> < 0.001 Primary safety outcome: apixaban vs. ASA: HR 1.13 (95% CI: 0.74–1.75); <i>P</i> = 0.57

<p>ENGAGE AF-TIMI 48 (www.clinicaltrials.gov, NCT00781391)⁴⁵</p> <p>Randomized, double-blind, double-dummy, parallel group, multicentre, multi-national non-inferiority trial</p>	<p>Pts ($n = 20\,500$) with NVAf and prior stroke/TIA or ≥ 2 of: CHF, hypertension, age ≥ 75 yrs, diabetes mellitus</p> <p>(1) Double-blind edoxaban 30 mg od^b (2) Double-blind edoxaban 60 mg od^b (3) Double-blind warfarin (INR 2–3)</p>	<p>Primary efficacy endpoint: composite of stroke and SE</p> <p>Primary safety outcome: major and non-major clinically relevant bleeding</p>	<p>Trial estimated to complete March 2012</p>
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^aAfter 10% enrolment with 2 risk factors, all subsequent patients were required to have ≥ 3 risk factors or a prior stroke/TIA

^bDoses halved for patients with ≥ 1 of the following creatinine clearance 30–50 mL/min, body weight ≤ 60 kg, or concomitant administration of verapamil or quinidine

ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ASA, acetylsalicylic acid; bid, twice daily; AVERRONES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or are Unsuitable for Vitamin K Antagonist Treatment; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; ENGAGE AF, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; g/dL, grams per decilitre; Hb, haemoglobin; HR, hazard ratio; INR, international normalized ratio; LVEF, left ventricular ejection fraction; mg/day, milligrams per day; NVAf, non-valvular atrial fibrillation; NYHA, New York Heart Association; od, once daily; PAD, peripheral artery disease; pts, patients; RBCs, red blood cells; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKEF AF, Rivaroxaban Once daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonist for prevention of stroke and Embolism Trial in Atrial Fibrillation; RR, relative risk; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist; warf, warfarin; yrs, years.

Phase III trials of the novel oral anticoagulants are also summarized in *Table 3*.

Oral direct thrombin inhibitors

Factor IIa (thrombin) is responsible for converting fibrinogen into fibrin and thus represents the final step in the coagulation pathway. In recent years, novel, oral direct thrombin inhibitors have been developed, some of which have been extensively evaluated in patients with AF.

Ximelagatran

Ximelagatran was the first oral anticoagulant to become available since the introduction of warfarin, and was approved in 22 countries (mostly European, but also including Argentina, Brazil, Hong Kong, and Indonesia) for the prevention of venous thromboembolism following total hip or knee replacement.^{46,47} In AF, the Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) trials III and V demonstrated that ximelagatran was at least as effective as warfarin (INR 2.0–3.0) for the primary outcome (all stroke or systemic embolism). No difference was seen between the treatment groups for rates of major bleeding.^{48,49} However, clinical development of ximelagatran was stopped and it was withdrawn from the market following reports of hepatotoxicity.^{46,47,50} Despite this, it demonstrated the feasibility of using an oral, fast-acting anticoagulant that did not require routine coagulation monitoring in patients with AF.⁵⁰

Dabigatran

Dabigatran is an oral direct thrombin inhibitor provided as a prodrug, dabigatran etexilate. Dabigatran has a bioavailability of around 7% after oral administration of dabigatran etexilate,⁵¹ and a half-life of up to 17 h.⁵² More than 80% of systemically available dabigatran is excreted renally.⁵¹

In the phase III Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) non-inferiority trial,^{37,38} patients with non-valvular AF ($n = 18\,113$) were randomized to receive two fixed doses of dabigatran [110 mg twice daily (bid) or 150 mg bid] in a blinded fashion, while the warfarin dose-adjusted (INR 2.0–3.0) arm was open label. The mean CHADS₂ score at baseline was 2.1, and when baseline scores were grouped into three categories (0–1, 2, and 3–6), approximately one-third of patients fell into each category. Approximately 20% of patients had experienced a previous stroke or TIA at baseline. The median follow-up duration was 2 years. The 150 mg bid dose showed superior efficacy to warfarin for the primary endpoint of stroke or systemic embolism [1.11 vs. 1.71% per year; RR 0.65 (95% CI 0.52–0.81); $P < 0.001$ for superiority], and the 110 mg bid dose achieved non-inferiority [1.54 vs. 1.71% per year; RR 0.90 (95% CI 0.74–1.10); $P < 0.001$ for non-inferiority], but not superiority (*Table 3*). Similar rates of all-cause mortality were seen across the groups. A greater number of myocardial infarctions was seen with both the 110 mg and 150 mg bid dose of dabigatran (98 and 97 events, respectively) compared with warfarin (75 events), although this did not reach statistical significance [110 mg vs. warfarin: RR 1.29 (95% CI 0.96–1.75; $P = 0.09$); 150 mg vs. warfarin: RR 1.27 (95% CI 0.94–1.71); $P = 0.12$]. The rate of major bleeding was

significantly lower with the 110 mg bid dose compared with warfarin [2.87 vs. 3.57% per year; RR 0.80 (95% CI 0.70–0.93); $P = 0.003$], and the higher dose showed no significant difference from warfarin [3.32 vs. 3.57% per year; RR 0.93 (95% CI 0.81–1.07); $P = 0.32$] (Table 3).^{37,38} A significantly higher rate of major gastrointestinal bleeding was seen with dabigatran 150 mg bid vs. warfarin

($P < 0.001$). Dyspepsia was also significantly more common in patients receiving dabigatran compared with warfarin ($P < 0.001$). Discontinuation rates were significantly higher in the dabigatran groups vs. the warfarin group at 1 year [15% (110 mg bid) and 16% (150 mg bid) vs. 10% (warfarin); $P < 0.001$] and at 2 years [21% (110 and 150 mg bid) vs. 17% (warfarin); $P < 0.001$]. The authors reported a significant net clinical benefit outcome (major vascular events, major bleeding, and death) with the 150 mg bid dose compared with warfarin [7.11 vs. 7.91% per year; RR 0.90 (95% CI 0.82–0.99); $P = 0.02$]. The results of the RE-LY study formed the basis of the approval of dabigatran 150 mg bid dose for the prevention of stroke and systemic embolism in patients with AF by the Food and Drug Administration (FDA).⁵³ However, the FDA also approved a 75 mg bid dose for patients with poor renal function (creatinine clearance of 15–30 mL/min), based on pharmacokinetic modelling data, but decided against approving the 110 mg bid dose.⁵⁴

Following FDA approval, dabigatran was the focus of an ACCF/AHA/HRS update to the ACC/AHA/ESC 2006 guidelines.⁵⁵ The update included dabigatran 150 mg bid as a useful alternative to warfarin (75 mg bid with creatinine clearance 15–30 mL/min). Consideration of individuals' abilities to comply with bid dosing, availability of anticoagulation monitoring facilities, preference, and cost is recommended when deciding to treat with dabigatran rather than warfarin. The update suggests that, because of the non-haemorrhagic side effects of dabigatran, patients already treated with warfarin with excellent INR control may derive little benefit from switching. In contrast to the US, however, the 150 mg bid and 110 mg bid doses were approved in Canada and the EU.^{56,57} The CCS 2010 guidelines recommend that most patients should receive dabigatran (150 mg bid) in preference to warfarin.¹² Unlike in the USA, the CCS 2010 guidelines also recommend the 110 mg dose for patients with decreased renal function, low body weight, or an increased risk of major bleeding.

A RE-LY subanalysis assessed the treatment effects of dabigatran compared with warfarin for secondary prevention in patients with prior stroke/TIA.⁵⁸ Consistent with the main study, both dabigatran doses were associated with lower rates of stroke/systemic embolism than warfarin (RR 0.84 for 110 mg and 0.75 for 150 mg). Once again, compared with warfarin, the rate of major bleeding was significantly lower with the 110 mg bid dose [RR 0.66 (95% CI 0.48–0.90)], and the higher dose showed no significant difference [RR 1.01 (95% CI 0.77–1.34)].⁵⁸ A network meta-analysis also indirectly compared dabigatran treatment with dual-antiplatelet therapy (ASA plus clopidogrel) for stroke prevention in patients with AF.⁵⁹ The 150 mg dabigatran dose was predicted to significantly reduce the risk of all stroke by 61% compared with dual-antiplatelet therapy (95% CI 0.21–0.72). The 110 mg dabigatran dose was estimated to reduce all stroke

risk [RR 0.55 (95% CI 0.30–1.00)] with a significant reduction in ischaemic stroke risk of 46% (95% CI 0.33–0.87), compared with dual-antiplatelet therapy. There was no signal of an increase in intracranial or extracranial haemorrhage with dabigatran compared with dual-antiplatelet therapy. Within the EU, the recommended dose of dabigatran is 150 mg bid, but a lower, 110 mg bid dose should be used in elderly patients (age ≥ 80 years) or those taking verapamil, and considered in patients with high bleeding risk, particularly in the presence of moderate renal impairment (creatinine clearance 30–50 mL/min). The drug should not be given to patients with severe renal impairment (creatinine clearance < 30 mL/min).⁶⁰

An extension of the RE-LY study, known as RELY-ABLE, is currently underway to assess the long-term safety of dabigatran in patients with AF (www.clinicaltrials.gov, NCT00808067). Patients who participated in RE-LY will receive further treatment for up to 28 months; at the time of writing, the estimated primary completion date (i.e. the final data collection date for the primary outcome measure of major bleeding) is April 2013.

Other direct thrombin inhibitors in atrial fibrillation

AZD0837 is another direct thrombin inhibitor in development. Phase II dose-ranging studies of AZD0837 extended-release [150–450 mg once daily (od)] and immediate-release (150 or 350 mg bid) formulations report that it is generally well tolerated in patients with non-valvular AF.^{61,62} At the time of writing, it is not known if a phase III trial is planned.

Oral direct Factor Xa inhibitors

In the search for effective oral anticoagulants, targeting factors 'upstream' from thrombin in the coagulation pathway, and thus inhibiting its generation, has become a prime focus. Factor Xa is of particular interest, given that it is the point where both the intrinsic and extrinsic coagulation pathways converge. Several oral direct Factor Xa inhibitors have been developed, a number of which have been approved or are currently in the advanced stages of testing in patients with AF.

Rivaroxaban

Rivaroxaban is a novel, oral, direct Factor Xa inhibitor. A 10 mg oral dose has a reported absolute bioavailability of 80–100%; elimination from the plasma occurs with terminal half-lives of 5–9 h in young individuals and 11–13 h in the elderly.^{63–65} Two-thirds of the drug undergoes metabolic degradation in the liver (half of which is excreted renally and half via the faecal route); one-third is eliminated renally as unchanged drug.^{66,67}

The Rivaroxaban Once daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) completed in late 2010. This phase III, double-blind, double-dummy study was designed to assess the efficacy and safety of rivaroxaban compared with adjusted-dose warfarin for the prevention of stroke and non-CNS systemic embolism (the composite primary efficacy endpoint) in patients with non-valvular AF at increased risk of stroke.^{39,40} Patients were required to have prior stroke, TIA, or systemic embolism, or two or more of the following risk factors for study inclusion: clinical heart failure and/or left ventricular

ejection fraction $\leq 35\%$, hypertension, age ≥ 75 years, or diabetes mellitus (Table 3). Patients were given rivaroxaban 20 mg od with oral warfarin placebo od (target sham INR 2.5, range 2.0–3.0), or oral warfarin od (target INR 2.5, range 2.0–3.0) plus oral rivaroxaban placebo od. Patients with impaired renal function (estimated creatinine clearance 30–49 mL/min) at randomization received a lower dose of rivaroxaban (15 mg od). The study was powered to determine non-inferiority of rivaroxaban compared with warfarin for prevention of the primary efficacy endpoint. The test for non-inferiority was conducted in the per-protocol population for the period when patients were receiving study drug.^{39,40} If non-inferiority was met, the possibility of superiority would then be assessed in the safety population while receiving study drug. Sensitivity analyses in the intention-to-treat (ITT) population were also performed. Over 14 000 patients were randomized at 1100 sites across 45 countries.⁴⁰

The mean CHADS₂ score for patients who underwent randomization was 3.5; 55% of patients had had a previous stroke, systemic embolism, or TIA.⁴⁰ Rivaroxaban was indeed found to be non-inferior to warfarin (Table 3). Furthermore, the subsequent analysis in the safety population reported rivaroxaban to be superior to warfarin while on treatment for the same endpoint [hazard ratio (HR) 0.79 (95% CI 0.65–0.95); $P = 0.02$] (Table 3).⁴⁰ In the sensitivity analyses (which included analysis periods both on and off study drug), rivaroxaban showed equivalence to warfarin (Table 3).⁴⁰ The investigators also reported a significant reduction in the composite secondary efficacy endpoint of vascular death, stroke, or embolism [HR 0.86 (95% CI 0.74–0.99); $P = 0.034$], for haemorrhagic stroke ($P = 0.024$) and non-CNS systemic embolism ($P = 0.003$) with rivaroxaban in the safety population.⁴⁰ Rates of major and non-major clinically relevant bleeding events were similar between the two groups (Table 3), although there were significant reductions in the rates of intracranial haemorrhage ($P = 0.02$), critical organ bleeding ($P = 0.007$), and bleeding-related death ($P = 0.003$) in the rivaroxaban group.⁴⁰ In contrast, there were significant increases in the rates of haemoglobin fall of ≥ 2 g/dL ($P = 0.02$) or transfusion need ($P = 0.04$) in the rivaroxaban group compared with warfarin. Major bleeding from a gastrointestinal site was also more common in the rivaroxaban group compared with the warfarin group (3.2% vs. 2.2%; $P < 0.001$).⁴⁰ Based on the findings of the ROCKET AF trial, rivaroxaban was recently approved for stroke prevention in patients with non-valvular AF in the US and in the EU.^{68,69}

In May 2011, the results of a subanalysis from those patients in ROCKET AF with a prior stroke or TIA were presented at the European Stroke Conference in Hamburg.^{70,71} The relative efficacy and safety profiles of rivaroxaban compared with warfarin were consistent with those seen in the overall trial population. Another subgroup analysis assessed the efficacy and safety of rivaroxaban in patients with moderate renal impairment (creatinine clearance 30–49 mL/min) who received rivaroxaban 15 mg od.⁷² Higher rates of stroke and overall bleeding were reported in patients with moderate renal impairment versus those without, but the subanalysis also found that the efficacy and safety of rivaroxaban versus warfarin were consistent with those of the overall ROCKET AF population receiving the 20 mg od dose. This is reflected in the recent EU summary of product characteristics

for rivaroxaban, where the 15 mg od dose is recommended in patients with moderate renal impairment (creatinine clearance 30–49 mL/min). It can also be used with caution in those with severe renal impairment (creatinine clearance 15–29 mL/min), but is not recommended in patients with creatinine clearance < 15 mL/min.⁷³

Apixaban

Apixaban is an oral, direct, selective Factor Xa inhibitor with an oral bioavailability of $\sim 50\%$ ⁷⁴ and a half-life of ~ 8 –15 h in healthy subjects.⁷⁵ Much of the drug is removed from the body via the faeces, with $\sim 25\%$ excreted renally.⁷⁵ The findings of two phase III studies, Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) and Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES), have recently been reported (Table 3).^{41–44} ARISTOTLE was a double-blind, non-inferiority trial comparing apixaban 5 mg (or 2.5 mg in selected patients) bid with warfarin (target INR 2.0–3.0) in 18 201 patients with AF and at least one risk factor for stroke.^{41,42} The mean CHADS₂ score for patients in the ARISTOTLE trial was 2.1 ± 1.1 , with less than 20% of patients having a prior stroke, TIA, or systemic embolism.⁴² There was a significant reduction in the rate of stroke or systemic embolism with apixaban compared with warfarin [HR 0.79 (95% CI 0.66–0.95); $P = 0.01$ for superiority (ITT analysis)]. The investigators also reported significantly lower rates of major bleeding [HR 0.69 (95% CI 0.60–0.80); $P < 0.001$], intracranial haemorrhage [HR 0.42 (95% CI 0.30–0.58); $P < 0.001$], and all-cause mortality [HR 0.89 (95% CI 0.80–0.99); $P = 0.047$] with apixaban compared with warfarin.⁴² Fewer myocardial infarctions and gastrointestinal bleeding events were observed with apixaban versus warfarin, but these were not statistically significant ($P = 0.37$).⁴²

AVERROES was a superiority trial in patients ($n = 5599$) who had failed or were unsuitable for VKA prophylaxis, comparing apixaban 5 mg (or 2.5 mg in selected patients) bid with ASA (81–324 mg per day).^{43,44} As with ARISTOTLE, the primary efficacy endpoint was the occurrence of stroke (ischaemic or haemorrhagic) or systemic embolism. AVERROES was terminated early following evidence from the interim analysis that apixaban was more effective than ASA.⁴⁴ In AVERROES, the risk of primary endpoint occurrence was significantly reduced with apixaban compared with ASA [HR 0.45 (95% CI 0.32–0.62); $P < 0.001$] (Table 3).⁴⁴ The major haemorrhage rate was not significantly higher with apixaban compared with ASA (Table 3). At the time of writing, apixaban is not yet approved for stroke prevention in patients with AF.

Edoxaban

Edoxaban (previously known as DU-176b) is an oral, direct, selective Factor Xa inhibitor also in clinical development for patients with AF. A phase III trial, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation (ENGAGE AF-TIMI 48), is currently underway (Table 3). This compares the efficacy and safety of two doses of edoxaban (30 and 60 mg od) with warfarin in ~ 20 500 patients with AF and a moderate-to-high risk of stroke over 24

months (www.clinicaltrials.gov, NCT00781391).⁴⁵ The primary endpoint is also the composite of stroke and systemic embolic events. The trial is estimated to be completed in March 2012.

Other direct Factor Xa inhibitors

Betrixaban and darexaban (formerly YM150) also directly target Factor Xa. Both were in the early stages of clinical testing in patients with AF; however, it was announced in September 2011 that development of darexaban was to be stopped.⁷⁶

The EXPLORE-Xa phase II dose-finding study compared three doses of betrixaban (40, 60, and 80 mg) with open-label, adjusted-dose warfarin (INR 2.0–3.0) in patients with non-valvular AF or atrial flutter ($n = 508$) (www.clinicaltrials.gov, NCT00742859).⁷⁷ The incidence of major and non-major clinically relevant bleeding (the primary endpoint) was reported to be lower than warfarin for the 40 mg dose and comparable to warfarin for the 60 and 80 mg doses. In a measure of drug activity, there was a small but statistically significant increase in D-dimer (a potential marker of thrombosis) with the 40 mg dose compared with warfarin ($P = 0.003$). The investigators attributed this increase to the use of warfarin as a comparator (as much-reduced D-dimer levels would be expected following conventional warfarin therapy in any case). Gastrointestinal disturbances (diarrhoea, nausea, and constipation) were also more commonly reported among those given the two higher doses of betrixaban vs. those on warfarin.

The safety and tolerability of darexaban in patients with AF were investigated in the phase II OPAL-1 and OPAL-2 studies.^{78,79} In the OPAL-1 trial, four doses of darexaban (30, 60, 120, and 240 mg od) were compared with open-label warfarin, administered over 12 weeks, in patients with non-valvular AF ($n = 448$) in the Asia-Pacific region.⁷⁸ Similar incidences of major and non-major clinically relevant bleeding to warfarin were seen with the 30, 60, and 120 mg doses of darexaban. No thromboembolic strokes were reported during the treatment period. In the larger OPAL-2 trial, 1297 patients with non-valvular AF were also randomized to various doses of darexaban (15 mg bid, 30 mg od, 30 mg bid, 60 mg od, 60 mg bid, or 120 mg od) or adjusted-dose warfarin.⁷⁹ Across the full dose range, darexaban showed fewer bleeding events compared with warfarin. Annual event rates for the composite efficacy endpoint (which included ischaemic stroke, TIA, systemic embolism, acute coronary syndrome, and/or any deaths) decreased as the dose increased [1.1–6.7% per year (darexaban) vs. 1.8% per year (warfarin)].⁷⁹

Indirect Factor Xa inhibitors

There have also been moves in recent years to develop new parenterally administered indirect Factor Xa inhibitors. In the phase III AMADEUS trial, idraparinux (2.5 mg weekly) was non-inferior to adjusted-dose warfarin in patients with AF for the primary efficacy endpoint (all stroke and systemic embolism). However, the trial was stopped early because of excess bleeding with idraparinux.⁸⁰

A biotinylated version, idrabiotaparinux, was also in clinical development for patients with AF, but this has now ceased.⁸¹

Conclusions

Current VKA therapy is highly effective at preventing stroke in patients with non-valvular AF. However, this benefit is offset by

the likelihood of bleeding associated with its use, as well as the need for regular coagulation monitoring because of high inter- and intra-subject variability and a sensitivity to drug interactions. Acetylsalicylic acid is associated with fewer bleeding events than VKA therapy but is far less efficacious. In general, trials of dual-antiplatelet therapy or combined antiplatelet and low- or moderate-intensity VKA therapy in patients with AF have proved disappointing.

Newer oral anticoagulants have the potential to simplify stroke prevention in patients with AF. Despite differences in study design, the phase III trials in patients with AF published to date for three of the newer agents (RE-LY, ROCKET AF, and ARISTOTLE) drew broadly similar conclusions.⁸² Rates of stroke and systemic embolism with the newer agents were at the very least comparable to those of warfarin. Favourable bleeding profiles compared with warfarin were reported across the trials, and there was an indication of reduced mortality compared with warfarin (reaching statistical significance in the ARISTOTLE trial).

The newer agents may therefore overcome the limitations associated with VKAs and provide an alternative to agents like warfarin. Collectively, the new agents may also lead to improved adherence to clinical guidelines when oral anticoagulation is the recommended option (although the degree to which they are successful in this may differ between the agents). This may in turn reap substantial benefits in terms of reducing the clinical and economic burden of stroke.

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