# Anticoagulant therapy for patients with ischaemic stroke

*Graeme J. Hankey*

**Abstract** | Anticoagulant therapy for ischaemic stroke aims to prevent recurrent ischaemic stroke and venous thromboembolism. Several large clinical trials have provided insight into the safety and efficacy of anticoagulant therapies. Anticoagulant treatment provides no net benefit over placebo or antiplatelet therapy in patients with acute ischaemic stroke of arterial or cardiac origin, because reductions in early recurrent ischaemic events and venous thromboembolism are offset by increases in bleeding events. For patients with ischaemic stroke of cardiac origin due to atrial fibrillation, long-term warfarin treatment reduces the risk of recurrent stroke by two-thirds compared with control, and by half compared with antiplatelet therapy. New anticoagulants, such as dabigatran, rivaroxaban and apixaban, are as efficacious and safe as warfarin, and have a rapid onset of action, few drug interactions, and predictable anticoagulant effects that do not require routine monitoring. However, the anticoagulant effects of the new drugs cannot be reliably measured or rapidly reversed in the event of major non-compressible bleeding or urgent surgery. In addition, the new agents cannot be used in patients with severe renal impairment or active liver disease. Ongoing research aims to resolve these limitations, examine whether the promising results of clinical trials can be translated into clinical practice, and monitor the long-term safety of anticoagulant therapies.

Hankey, G. J. *Nat. Rev. Neurol.* **8**, 319–328 (2012); published online 8 May 2012; doi:10.1038/nrneurol.2012.77

## Introduction

For patients with ischaemic stroke or transient ischaemic attack (TIA) caused by *in situ* arterial thrombosis or thromboembolism, anticoagulant therapy is used to prevent recurrent ischaemic stroke and venous thromboembolism. For patients with ischaemic stroke or TIA and atrial fibrillation, anticoagulant intervention with oral vitamin K antagonists (VKAs), such as warfarin, has been the mainstay of treatment to prevent recurrent stroke. Long-term warfarin treatment is highly effective when given at an optimal dose maintaining the international normalized ratio (INR) within the therapeutic range (INR 2–3). However, this drug is substantially underused owing to concerns over the risk of bleeding and, when it is used, the dose is generally lower or higher than is required to maintain the INR within the therapeutic range, mainly because of pharmacological limitations, such as interactions with food and other drugs that alter the metabolism of warfarin (Table 1).[1–7]

Suboptimal use of warfarin has serious consequences: for every 10% reduction in time in the therapeutic range (TTR) of the INR, the absolute annual risk of stroke is increased by 1%.[6] Furthermore, the severity of strokes caused by atrial fibrillation, which could have been prevented by appropriate and optimal use (INR 2–3) of anticoagulant treatment, is particularly high. One study showed that at 3–6 months' follow-up, 73% of patients with ischaemic stroke caused by atrial fibrillation had died or were dependent on others to perform daily activities.[8] The underuse and suboptimal use of warfarin in patients with atrial fibrillation and at risk of stroke has prompted the development and evaluation of three new oral anticoagulants for stroke prevention: the direct thrombin inhibitor dabigatran, and the activated factor X inhibitors rivaroxaban and apixaban (Figure 1).[9,10] This article provides an updated review of the evidence for the safety and efficacy of anticoagulant therapies in prevention of recurrent ischaemic stroke caused by arterial and cardiac thromboembolism, and discusses the implications of the available data for clinical practice.

## Clinical trials

A systematic review and meta-analysis of all published and unpublished randomized controlled trials (RCTs) provides the highest level of evidence for the efficacy and safety of a therapeutic intervention, such as anticoagulant drugs in stroke prevention.[11] Most RCTs of anticoagulant drugs for stroke prevention have assessed the effectiveness of these drugs compared with placebo or antiplatelet therapy in the prevention of 'early' or 'long-term' recurrent stroke. Early recurrent strokes occur within the first 2 weeks after the onset of ischaemic stroke when there is a risk of haemorrhagic transformation of the infarcted brain, whereas 'long-term' recurrent strokes occur after the first 2 weeks and recur for several years. Several RCTs

**Competing interests**
G. J. Hankey declares associations with the following companies: Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Johnson & Johnson, Pfizer, Sanofi-Aventis. See the article online for full details of the relationships.

Department of Neurology, Royal Perth Hospital, 197 Wellington Street, Perth, WA 6001, Australia.
graeme.hankey@uwa.edu.au

**Key points**

- Anticoagulant therapy aims to prevent recurrent ischaemic stroke and venous thromboembolism
- Anticoagulant drugs do not benefit patients with acute ischaemic stroke of presumed arterial or cardiac origin, but long-term treatment with these drugs benefits patients with ischaemic stroke of presumed cardiac origin
- The oral anticoagulant drug warfarin is inexpensive, widely accepted and effective when used at an optimal dose, but monitoring and adverse reactions are a burden for patients and health-care providers
- The oral thrombin inhibitor dabigatran and the activated factor X inhibitors rivaroxaban and apixaban are as safe and effective as warfarin, and carry significantly less risk of intracranial haemorrhage
- The new oral anticoagulant drugs (dabigatran, rivaroxaban and apixaban) have rapid onset of action, few drug interactions and predictable anticoagulant effects that do not require routine monitoring
- The effects of the new anticoagulant drugs cannot be reliably measured or rapidly reversed, their use is contraindicated in patients with renal impairment, and their long-term safety is unknown

of anticoagulant drugs for stroke prevention only included patients with ischaemic stroke or TIA of presumed arterial or cardiac origin. The reason for selecting these patient groups is that the effectiveness of the anticoagulant drugs in preventing recurrent strokes partly depends on the site and nature of the thrombus that caused the initial stroke.

Antiplatelet drugs are effective in preventing the formation of predominantly 'white' platelet clots in areas of high shear stress, such as arteries (for example, in ischaemic stroke or TIA caused by arterial atherothromboembolism). However, anticoagulant drugs have been shown to effectively prevent the formation of predominantly 'red' fibrin clots in areas of reduced and stagnant blood flow, such as in cardiac chambers with impaired contractility (for example, in the fibrillating left atrium or akinetic left ventricle), or in the veins of a paralysed leg.[12]

### Early recurrent stroke of arterial origin

In a systematic review of 24 RCTs involving 23,748 patients with acute ischaemic stroke of presumed arterial origin, early anticoagulant treatment (within the first few days of the stroke) was associated with a reduction in incidence of recurrent ischaemic stroke in the next few weeks compared with no anticoagulant treatment (placebo or another antiplatelet drug; Table 2).[13] However, anticoagulant treatment was also associated with an increase in incidence of symptomatic intracranial haemorrhage (Table 2). Consequently, early anticoagulant therapy produced no net benefit in reducing the odds of any type of recurrent stroke. Early initiation of treatment was associated with a reduction in the occurrence of—mostly asymptomatic—deep vein thrombosis (DVT) and symptomatic pulmonary embolism, but these benefits were offset by an increase in major extracranial haemorrhage (Table 2). Overall, anticoagulant drugs failed to reduce the odds of mortality or disability at the end of the follow-up period (ranging from 12 days to 1 year) compared with controls. Mortality and disability rates were consistent among all types of anticoagulant drugs used; for example, unfractionated heparin (OR 1.00, 95% CI 0.94–1.06), low molecular weight heparin (LMWH; OR 0.82, 95% CI 0.64–1.04) and heparinoids (OR 0.92, 95% CI 0.72–1.19), although another systematic review indicated that LMWHs, danaparoid or enoxaparin, and heparinoids were more effective than standard unfractionated heparin for preventing DVT (13% versus 22%, OR 0.55, 95% CI 0.44–0.70).[14]

Subsequent to the above-mentioned systematic reviews and meta-analyses,[13,14] the Fraxiparin in Stroke Study for the treatment of ischaemic stroke (FISS-tris)[15] reported no superiority of LMWH over aspirin for the primary end point—score on the Barthel Index (a scale used to measure performance in activities of daily living)—in 603 Asian patients with acute ischaemic stroke caused by large artery occlusive disease. However, a subgroup analysis has raised the hypothesis that, compared with aspirin, LMWH might benefit certain subgroups of patients with acute cerebral infarct and large-artery occlusive disease, such as the patients in FISS-tris who were over 68 years old, had symptomatic posterior circulation arterial disease, and did not receive any antiplatelet treatment on admission.[16] Further studies will be required to test this hypothesis.

### Long-term recurrent stroke of arterial origin

According to a systematic review of 11 RCTs involving 2,487 patients with ischaemic stroke or TIA of presumed arterial origin, a prolonged course (at least 1 month) of anticoagulant therapy, such as warfarin, did not reduce the risk of recurrent ischaemic stroke compared with control. However, prolonged anticoagulant therapy did increase the risk of fatal intracranial haemorrhage (OR 2.54, 95% CI 1.19–5.45, absolute risk increase [ARI] 1.1%) and major extracranial haemorrhage (OR 3.43, 95% CI 1.94–6.08, ARI 2.3%).[17]

### Early recurrent stroke of cardiac origin

In a systematic review of seven RCTs involving 4,624 patients with acute ischaemic stroke of presumed cardiac origin (3,797 patients with atrial fibrillation and 827 with other mixed cardioembolic causes), early anticoagulant therapy (within 48 h of stroke) with unfractionated heparin, LMWH or heparinoids did not significantly reduce the incidence of recurrent ischaemic stroke within 7–14 days of initial stroke, and did not reduce mortality and disability rates, but did significantly increase the occurrence of symptomatic intracranial bleeding compared with patients who did not receive early anticoagulant therapy (2.5% versus 0.7%, OR 2.89, 95% CI 1.19–7.01, ARI 1.8%).[8] However, in patients who have a high risk of early recurrent cardioembolic ischaemic stroke (defined by high $CHADS_2$ score, and echocardiographic evidence of left ventricular systolic dysfunction and left atrial spontaneous echo contrast)[18,19] or a low risk of haemorrhagic transformation of the brain infarct (defined by small area of brain infarction and well-controlled blood pressure),[20,21] early anticoagulant treatment might be safe and effective. Further clinical trials are needed to determine which patients, if any, can benefit from anticoagulant therapy within the first 2 weeks of acute cardioembolic stroke.

**Table 1** | Properties of warfarin and new oral anticoagulant drugs

| Feature | Warfarin | Dabigatran | Rivaroxaban | Apixaban |
|---|---|---|---|---|
| Target | Vitamin K epoxide reductase complex Coagulation factors II, VII, IX and X | Thrombin | Activated coagulation factor X | Activated coagulation factor X |
| Dosing | Adjusted to INR of 2–3 | Fixed (110 mg or 150 mg), twice-daily* | Fixed (20 mg), once-daily | Fixed (5 mg), twice-daily |
| Oral bioavailability | 93% | 6–7% | 80% | 50% |
| Onset of action | 4–7 days | 0.5–2 h | 3–4 h | 3–4 h |
| Time to peak plasma concentration | 4 h | 2 h | 3 h | 3 h |
| Duration of peak plasma concentration | 24–72 h | 0.5–2.0 h | 2.5–4 h | 3–4 h |
| Plasma protein binding | 99% | 35% | 95% | 87% |
| Half-life | 20–60 h | 11–15 h | 7–13 h | 10–14 h |
| Duration of action | 48–96 h | 24 h | Not reported | Not reported |
| Interactions | Food‡ and drugs§ | Potent inhibitors of P-glycoprotein‖ | Potent inhibitors of P-glycoprotein‖ and cytochrome p450 3A4¶ | Potent inhibitors of cytochrome p450 3A4¶ |
| Excretory route | Renal (92% as metabolites) | Renal (80%) | Renal (66%; half unchanged, half as metabolites) Faeces and biliary (33% as metabolites) | Renal (25%) Faeces (20%) |
| Adverse effects (>1%) | Bleeding | Dyspepsia, bleeding | Bleeding | Bleeding |
| Monitoring | INR measurement (every 1–4 weeks) | INR measurement not required Activated partial thromboplastin time, thrombin time and ecarin clotting time can be measured | INR measurement not required Prothrombin time, and anti-activated factor X activity can be measured | INR measurement not required Prothrombin time and antiactivated factor X levels can be measured |
| Antidote | Rapid reversal with fresh frozen plasma Prothrombin complex concentrate Recombinant coagulation factor VII Slow reversal with vitamin K | Dialysis | None available | None available |
| Cost | US$1–2 per day | Likely to be more expensive, but cost-effective | Likely to be more expensive, but cost-effective | Likely to be more expensive, but cost-effective |
| Familiarity | Extensive | Minimal | Minimal | Minimal |

*Dependent on indication, creatinine clearance, age, and concomitant use of P-glycoprotein inhibitors. ‡Spinach, brussels sprouts, parsley and green tea are rich sources of vitamin K that can lower, whereas alcohol and cranberry juice can increase, warfarin's effectiveness. §Antibiotics (such as cotrimoxazole and metronidazole), antifungals (such as fluconazole), antidepressants (such as selective serotonin reuptake inhibitors), antiplatelet drugs (such as aspirin and clopidogrel), amiodarone, anti-inflammatory drugs, paracetamol, and alternative remedies (Gingko biloba and chamomile) can increase, and rifampicin and St John's wort can decrease, warfarin's effectiveness. ‖P-glycoprotein inhibitors including azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, posaconazole) and protease inhibitors (e.g. ritonavir). ¶Cytochrome p450 isoenzyme inhibitors, such as azole antifungals, protease inhibitors (e.g. atanazavir), and macrolide antibiotics (e.g. clarithromycin). Abbreviation: INR, international normalized ratio.

## Long-term recurrent stroke of cardiac origin

### *Warfarin*

In two RCTs including 485 individuals with prior ischaemic stroke or TIA and atrial fibrillation, an adjusted dose of warfarin (INR 2–3) reduced the risk of recurrent stroke by two-thirds compared with control (3.9% per year with warfarin versus 12.3% per year with control, HR 0.34, 95% CI 0.20–0.57, absolute risk reduction 8.4%) and was associated with an insignificant trend toward an increase in major bleeding (2.8% with warfarin versus 0.7% with control per year, HR 3.20, 95% CI 0.91–11.3).[22–24] Compared with antiplatelet therapy (aspirin or indobufen), an adjusted dose of warfarin was significantly more effective for preventing the occurrence of recurrent stroke (OR 0.49, 95% CI 0.33–0.72), but was associated with a higher risk of extracranial bleeding (OR 5.16, 95% CI 2.08–12.83) in 1,371 individuals with prior ischaemic stroke or TIA and atrial fibrillation.[24,25] Consistently, adjusted-dose warfarin (targeting an INR 2–3) was significantly more effective in reducing the risk of recurrent strokes than the combination of clopidogrel (75 mg once-daily) plus aspirin (75–100 mg daily) among 1,020 individuals with atrial fibrillation and prior stroke or TIA (2.99% with warfarin versus 6.22% with clopidogrel plus aspirin, relative risk [RR] 0.47, 95% CI 0.25–0.81).[26,27]

### *Dabigatran*

Dabigatran etexilate is a prodrug of the active moiety dabigatran—an oral, reversible, direct inhibitor of thrombin (Figure 1, Table 1).[9] After oral administration, dabigatran has a fast onset of action, reaching peak plasma concentrations within 0.5–2.0 h. Dabigatran has a low potential for food and drug interactions, a half-life of 11–15 h in patients with normal renal function, and a fast offset of action. About 80% of the drug is excreted unchanged by the kidneys.[9]

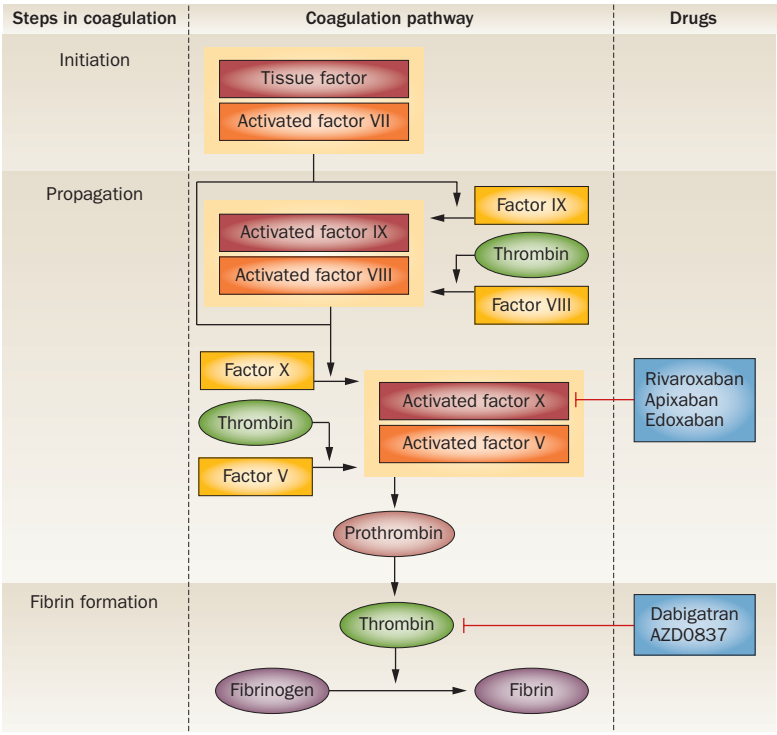


**Figure 1** | Schematic illustration of the actions of new anticoagulants in the coagulation cascade. Vessel injury exposes tissue factor, which interacts with activated factor VII to initiate coagulation. Cleavage of prothrombin by the prothrombinase complex (activated factor X and its cofactor, activated factor V) leads to the generation of thrombin. Thrombin converts fibrinogen to fibrin and provides positive feedback through activation of factors V, VIII, and XI in the coagulation cascade. Activated factors V, VIII, and XI promote the production of additional thrombin, which leads to cross-linkage of fibrin strands and the formation of a hemostatic plug. Thrombin also activates platelets through cleavage of the platelet-membrane–bound protease-activated receptors 1, 3, and 4. Activated factor X inhibitors (rivaroxaban, apixaban, edoxaban) block the conversion of prothrombin to thrombin. Thrombin inhibitors (dabigatran and ADZ0837) block thrombin-mediated conversion of fibrin. These drugs also block thrombin-mediated feedback activation of factors V and VIII.

**Table 2** | Effects of parenteral anticoagulants in acute ischaemic stroke[13]

| Outcome | Odds ratio versus control (95% CI) | Absolute risk versus control (95% CI) |
|---|---|---|
| Death or dependence | 0.99 (0.93–1.04) | Not significant |
| Death | 1.05 (0.98–1.12) | Not significant |
| Recurrent ischaemic stroke | 0.76 (0.65–0.88) | 0.9% reduction (0.4–1.3) |
| Symptomatic intracranial haemorrhage (dose-related) | 2.55 (1.95–3.33) | 0.9% increase (0.6–1.1) |
| Recurrent stroke of any type | 0.97 (0.85–1.11) | Not significant |
| Major extracranial haemorrhage (dose-related) | 2.99 (2.24–3.99) | 0.9% increase (0.7–1.2) |
| Deep vein thrombosis (mostly asymptomatic) | 0.21 (0.15–0.29) | 28.1% reduction (23.0–33.2) |
| Pulmonary embolism | 0.60 (0.44–0.81) | 0.4% reduction (0.1–0.6) |

The RE-LY (Randomized Evaluation of Long-term anticoagulant therapY) trial was a prospective, open-label, randomized trial with blinded evaluation of all outcomes (PROBE design), which aimed to determine whether dabigatran would be noninferior to warfarin in the prevention of stroke or systemic embolism among patients with atrial fibrillation (Table 3, Supplementary Table 1 online).[28,29] A total of 18,113 patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke, such as a history of previous ischaemic stroke, were randomly assigned to receive fixed doses of dabigatran (110 mg or 150 mg twice daily) in a blinded fashion or an adjusted dose of warfarin (INR 2–3) in an unblinded fashion for a median of 2 years. Intention to treat (ITT) analysis showed that the low dose of dabigatran (110 mg twice daily) was noninferior to warfarin and the high dose of dabigatran (150 mg twice daily) was superior to warfarin in reducing the rate of stroke or systemic embolism (Table 3). Major bleeding and fatal bleeding rates were significantly lower with the low dose of dabigatran and similar with the high dose of dabigatran, when compared with warfarin (Table 3).

Both doses of dabigatran were associated with significantly fewer incidences of intracranial bleeds compared with warfarin (Table 3).[28,29] However, the high dose of dabigatran significantly increased gastrointestinal bleeding compared with warfarin (1.56% versus 1.07% per year, RR 1.48, 95% CI 1.18–1.85) and low-dose dabigatran (1.56% versus 1.15% per year, RR 1.36, 95% CI 1.09–1.70).

Dabigatran caused higher rates of dyspepsia than did warfarin (Table 3), presumably related to the tartaric acid content of the dabigatran etexilate capsule.[28] Dabigatran was also associated with an increase in incidence of myocardial ischaemic events compared with warfarin.[30] Although the absolute rates of myocardial ischaemic events were low and the RE-LY trial was not powered to reliably identify or exclude an excess of myocardial ischaemic events, a recent meta-analysis of seven RCTs of dabigatran, including the RE-LY trial, suggests that dabigatran could increase the risk of myocardial ischaemic events and acute coronary syndrome (OR 1.33, 95% CI 1.03–1.71).[31] The overall results of RE-LY were consistent among the subgroup of 3,623 patients with prior stroke or TIA (Table 3).[32]

Dabigatran has been approved by the FDA, Canada, and the European Union for the prevention of stroke and systemic embolism in patients with paroxysmal or permanent atrial fibrillation and at least one risk factor for stroke, but without a prosthetic heart valve or haemodynamically significant valve disease, severe renal failure (creatinine clearance <30 ml/min) or advanced liver disease (impaired baseline clotting function).[9,33,34] The FDA approved the high dose (150 mg twice daily) but not the low dose of dabigatran, because of concerns that the low dose did not have any efficacy advantages over warfarin.[33] However, on the basis of pharmacokinetic modelling data, the FDA also approved a 75 mg twice-daily dose of dabigatran for patients with a creatinine clearance of 15–30 ml/min.

In the European guidelines, 150 mg dabigatran twice a day is recommended for patients at low risk of bleeding (HAS-BLED score 0–2), whereas 110 mg dabigatran twice a day is recommended for those at high risk of bleeding (HAS-BLED score ≥3).[35] In the Canadian guidelines, dabigatran is recommended as an alternative to warfarin for patients at all levels of risk for stroke.[36] The 150 mg dabigatran twice-daily treatment was recommended and

**Table 3** | Major events reported in clinical trials of the new oral anticoagulant drugs

| Events | RE-LY[28,29] | ROCKET[41] | ARISTOTLE[44] | AVERROES[51] |
|---|---|---|---|---|
| ***In patients with atrial fibrillation*** | | | | |
| Stroke or systemic embolism | Warfarin: 1.71% per year<br>Dabigatran 110 mg: 1.54% per year (RR 0.90, 95% CI 0.74–1.10, *P*<0.001 for noninferiority, *P*=0.30 for superiority)<br>Dabigatran 150 mg: 1.11% per year (RR 0.65, 95% CI 0.52–0.81, *P*<0.001 for superiority) | Warfarin: 2.16% per year<br>Rivaroxaban: 1.71% per year (HR, 0.79, 95% CI 0.66–0.96, *P*<0.001 for noninferiority, *P*=0.12 for superiority) | Warfarin: 1.60% per year<br>Apixaban: 1.27% per year (HR 0.79, 95% CI 0.66–0.95, *P*<0.001 for noninferiority, *P*=0.01 for superiority) | Aspirin: 3.70% per year<br>Apixaban: 1.60% per year (HR 0.45, 95% CI 0.32–0.62, *P*<0.001) |
| Major bleeding | Warfarin: 3.57% per year<br>Dabigatran 110 mg: 2.87% per year (RR 0.80, 95% CI 0.70–0.93, *P*=0.003)<br>Dabigatran 150 mg: 3.32% per year (RR 0.93, 95% CI 0.81–1.07, *P*=0.32) | Warfarin: 3.40% per year<br>Rivaroxaban: 3.60% per year (HR 1.04, 95% CI 0.90–1.20, *P*=0.58) | Warfarin: 3.09% per year<br>Apixaban: 2.13% per year (HR 0.69, 95% CI 0.60–0.80, *P*<0.001) | Aspirin: 1.20% per year<br>Apixaban: 1.40% per year (HR 1.13, 95% CI 0.74–1.75, *P*=0.57) |
| Intracranial haemorrhage | Warfarin: 0.76% per year<br>Dabigatran 110 mg: 0.23% per year (RR 0.30, 95% CI 0.19–0.45, *P*<0.001)<br>Dabigatran 150 mg: 0.31% per year (RR 0.41, 95% CI 0.28–0.60, *P*<0.001) | Warfarin: 0.74% per year<br>Rivaroxaban: 0.49% per year (HR 0.67, 95% CI 0.47–0.93, *P*=0.02) | Warfarin: 0.80% per year<br>Apixaban: 0.33% per year (HR 0.42, 95% CI 0.30–0.58, *P*<0.001) | Aspirin: 0.40% per year<br>Apixaban: 0.40% per year (HR 0.85, 95% CI 0.38–1.90, *P*=0.69) |
| Death from any cause | Warfarin: 4.13% per year<br>Dabigatran 110 mg: 3.75% per year (RR 0.91, 95% CI 0.80–1.03, *P*=0.13)<br>Dabigatran 150 mg: 3.64% per year (RR 0.88, 95% CI 0.77-1.00, *P*=0.051) | Warfarin: 4.50% per year<br>Rivaroxaban: 4.90% per year (HR 0.92, 95% CI 0.82–1.03, *P*=0.15) | Warfarin: 3.94% per year<br>Apixaban: 3.52% per year (HR 0.89, 95% CI 0.80–0.99, *P*=0.047) | Aspirin: 4.40% per year<br>Apixaban: 3.50% per year (HR 0.79, 95% CI 0.62–1.02, *P*=0.07) |
| Adverse effects (dyspepsia) | Warfarin: 5.8% per year<br>Dabigatran 110 mg: 11.8% per year<br>Dabigatran 150 mg: 11.3% per year | None reported | None reported | None reported |
| ***In patients with prior stroke or TIA**‡*** | | | | |
| Stroke or systemic embolism | Warfarin: 2.78% per year<br>Dabigatran 110 mg: 2.32% per year (RR 0.84, 95% CI 0.58–1.20, interaction *P*=0.62)<br>Dabigatran 150 mg: 2.07% per year (RR 0.75, 95% CI 0.52–1.08, interaction *P*=0.34) | Warfarin: 2.96% per year<br>Rivaroxaban: 2.79% per year (HR 0.94, 95% CI 0.77–1.16, interaction *P*=0.23) | Warfarin: 3.2% per year<br>Apixaban: 2.5% per year (interaction *P*=0.07) | Aspirin: 9.16% per year<br>Apixaban: 2.39% per year (HR 0.29, 95% CI 0.15–0.60, interaction *P*=0.17) |
| Major bleeding | Warfarin: 4.15% per year<br>Dabigatran 110 mg: 2.74% per year (RR 0.66, 95% CI 0.48–0.90, interaction *P*=0.15)<br>Dabigatran 150 mg: 4.15% per year (RR 1.01, 95% CI 0.77–1.34, interaction *P*=0.51) | Warfarin: 3.22% per year<br>Rivaroxaban: 3.13% per year (HR 0.96, 95% CI 0.87–1.07, interaction *P*=0.36) | Warfarin: 3.90% per year<br>Apixaban: 2.80% per year (interaction *P*=0.71) | Aspirin: 2.89% per year<br>Apixaban: 4.10% per year (HR 1.28, 95% CI 0.58–2.82, interaction *P*=0.73) |

*With prior stroke, TIA or systemic embolism in the RE-LY, ROCKET, ARISTOTLE and AVERROES trials. ‡*n*=3,623 (20%) in RE-LY trial, *n*=7,811 (54.8%) in ROCKET trial, *n*=3,538 (19.4%) in ARISTOTLE trial, and *n*=764 (13.6%) in AVERROES trial. Abbreviations: HR, hazard ratio; RR, relative risk, TIA, transient ischaemic attack.

a 110 mg dabigatran twice-daily regimen was specifically available for elderly patients (aged ≥80 years) and for patients at high risk of bleeding.[36]

No studies have directly compared dabigatran with placebo or antiplatelet therapy. However, in a network meta-analysis of all RCTs of antithrombotic treatments in patients with atrial fibrillation, indirect comparisons were performed of dabigatran with placebo and antiplatelet drugs.[37] These comparisons indicated that dabigatran at 150 mg twice daily may reduce the risk of stroke by 75% (RR 0.25, 95% CI 0.12–0.51) compared with placebo, by 63% (RR 0.37, 95% CI 0.20–0.69) compared with aspirin monotherapy, and by 61% (RR 0.39, 95% CI 0.21–0.72) compared with aspirin plus clopidogrel. This analysis also suggested that a high dose of dabigatran twice a day might not significantly increase the risk of intracranial or extracranial haemorrhage compared with aspirin monotherapy, or aspirin plus clopidogrel.

### *Rivaroxaban*

Rivaroxaban is an oral direct inhibitor of activated factor X that has a rapid onset of action (maximum plasma concentrations are reached after 3–4 h) and exhibits predictable, dose-proportional pharmacokinetics, with high oral bioavailability (Figure 1, Table 1).[38,39] Rivaroxaban has a dual mode of elimination; approximately one-third of the drug is eliminated unchanged by the kidneys, and two-thirds are metabolized by the liver.[40] Half of the metabolized fraction is excreted in urine and the other half excreted in faeces.[40] Rivaroxaban has a low propensity for drug–drug interactions, and no studies have reported food–drug interactions.

In the double-blinded ROCKET-AF trial (Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation), 14,264 patients with nonvalvular atrial fibrillation were randomly assigned to

rivaroxaban 20 mg once daily (15 mg/day if creatinine clearance 30–49 ml/min) or dose-adjusted warfarin (targeting a INR 2–3) for a median of 590 days (Supplementary Table 1 online).[41] The patients enrolled in the ROCKET-AF trial were at higher risk of stroke than those in the RE-LY, ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) and AVERROES (Apixaban versus Acetylsalicylic Acid to Prevent Strokes) trials. The mean $CHADS_2$ score was 3.5, and a history of stroke, TIA or systemic embolism was present in 55% of patients.[41] The primary analysis in ROCKET-AF was a per-protocol, on-treatment analysis. This method provides the most conservative means of testing for noninferiority in an RCT, because an ITT analysis could bias the result toward noninferiority if patients do not take their assigned treatment.[42,43] ITT analysis is, however, the most conservative method for assessing superiority in an RCT.[11]

Rivaroxaban was noninferior to warfarin for prevention of stroke or systemic embolism in the primary per-protocol, on-treatment analysis (Table 3). In ITT analysis, rivaroxaban was also noninferior, but not superior, to warfarin for preventing stroke or systemic embolism (2.12% versus 2.42% per year, HR 0.88, 95% CI 0.74–1.03, $P<0.001$ for noninferiority, $P=0.117$ for superiority).[43] Rates of major and non-major clinically relevant bleeding were similar in both groups (14.91% versus 14.52% risk of bleeding per year), whereas intracranial haemorrhage and fatal bleeding rates were significantly lower with rivaroxaban than with warfarin. By contrast, gastrointestinal bleeding occurred more frequently with rivaroxaban than with warfarin (3.15% versus 2.16%, $P<0.001$). Non-haemorrhagic adverse events were observed at similar rates across groups.[41] The relative treatment effects of rivaroxaban versus warfarin were consistent among patients with and without prior stroke or TIA (Table 3).[44]

Rivaroxaban was approved by the FDA and the European Union in 2011 for the prevention of stroke and systemic embolism in patients with atrial fibrillation.[45,46] Rivaroxaban has a boxed warning that people using the drug should not stop taking it before talking with their health-care provider. This warning could be related to the end result of the ROCKET-AF trial, which showed that when patients changed treatments from anticoagulant drugs to VKAs, the time to reach a therapeutic INR of at least 2 was longer for those previously assigned to rivaroxaban (median 13 days) than for those previously taking warfarin (median 3 days). In addition, the number of primary events (stroke or systemic embolism) occurring during the first month after termination of the anticoagulant treatment was significantly higher among patients who changed to VKA treatment from rivaroxaban than among those who changed from warfarin ($n=22$ for rivaroxaban and $n=7$ for warfarin, $P=0.008$).[41]

### *Apixaban*

Apixaban is an orally administered direct inhibitor of activated coagulation factor X (also known as thrombokinase) with rapid absorption, about 50% bioavailability, and a 12-h half-life (Figure 1, Table 1). Apixaban is metabolized mainly by the cytochrome p450 enzymes CYP3A4 and CYP3A5, and about 25% is excreted through the kidneys.[47–49] In individuals with renal impairment, apixaban plasma concentrations are increased by 16%, 29% and 44% in mild (creatinine clearance 51–80 ml/min), moderate (creatinine clearance 30–50 ml/min) and severe (creatinine clearance 15–29 ml/min) impairment, respectively, compared with individuals with normal creatinine clearance. No dose adjustment of apixaban treatment is required in patients with mild or moderate hepatic impairment. Apixaban has minimal potential for drug–drug interaction, except with strong CYP3A4 inhibitors, such as macrolide antibiotics, azole antifungals and protease inhibitors, which substantially increase blood concentrations of apixaban.[47]

In the ARISTOTLE trial, 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke, such as a history of previous ischaemic stroke, were randomly assigned to apixaban (5 mg twice daily) or warfarin (target INR 2–3) in a double-blind fashion for a median duration of 1.8 years (Supplementary Table 1 online).[50] Apixaban was superior to warfarin in reducing the rate of stroke or systemic embolism (Table 3). Apixaban also caused significantly less major bleeding, less intracranial haemorrhage, and less mortality than warfarin in these patients.[50] The relative treatment effects of apixaban versus warfarin were consistent among patients with or without prior stroke or TIA (Table 3).[50]

In the AVERROES trial (Supplementary Table 1 online), which investigated the superiority of apixaban over aspirin, 5,599 patients with atrial fibrillation at increased risk of stroke and for whom VKA therapy was unsuitable were randomly assigned to double-blinded treatment with apixaban (5 mg twice daily) or aspirin (81–324 mg daily).[51] After a mean follow up of 1.1 years, the trial was terminated early, as a substantial benefit was observed with apixaban in terms of reducing the rate of the primary outcome of stroke or systemic embolism (Table 3). The occurrence of major and intracranial bleeding was not significantly different between the apixaban and aspirin groups (Table 3). Apixaban was better tolerated than aspirin, as indicated by a lower rate of permanent discontinuation (17.9% annual discontinuation for apixaban versus 20.5% for aspirin, HR 0.88, 95% CI 0.78–0.99).[51] The relative effects of apixaban versus aspirin were consistent among patients with and without prior stroke or TIA (Table 3).[52]

### Interpretation of clinical trial results

The results of the RE-LY, ROCKET-AF, ARISTOTLE and AVERROES trials are remarkable in that they all showed that the new anticoagulant drugs, dabigatran, rivaroxaban and apixaban, were noninferior to warfarin. Moreover, in the AVERROES trial, apixaban was superior to aspirin. These findings are impressive given the extraordinary efficacy of the comparator drug, warfarin, in preventing stroke by two-thirds compared with placebo. Moreover, each new anticoagulant drug achieved its effects without increasing major bleeding or risk of other serious adverse effects, except for a possible small increase in

the risk of myocardial ischaemic events with dabigatran. Indeed, each new anticoagulant drug produced significantly lower rates of intracranial haemorrhage—the most life-threatening complication of anticoagulant therapy—than warfarin. Whether this effect reflects poor INR control among patients treated with warfarin or a tendency for warfarin to cause or exacerbate intracerebral haemorrhage is not known; further analyses of trial data are awaited.[53,54]

For patients assigned to warfarin treatment, the mean TTR was lower in the ROCKET-AF trial (55%) than in the RE-LY (64%) or ARISTOTLE (62%) trials (Supplementary Table 1 online). This difference could be attributable to higher proportion of patients with heart failure (62%) and a more conservative definition of TTR in the ROCKET-AF trial than in the other trials.[28,41,50] In the ROCKET-AF trial,[41] the TTR was calculated from all INR values measured during the study and for 7 days after warfarin treatment was interrupted.[41] By contrast, in the RE-LY and ARISTOTLE trials, the TTR was calculated after excluding INR values measured during the first week after patient randomization and after discontinuation of the study drug.[28,50] Nevertheless, the differences in TTR values among the three trials did not affect the primary results; the benefits of the new anticoagulant drugs dabigatran, apixaban and rivaroxaban were consistent, irrespective of the inter-trial differences in the TTR calculations among patients assigned to warfarin.[41,55] The results of the RE-LY, ROCKET-AF and ARISTOTLE trials were also consistent among other patient subgroups, including those with atrial fibrillation and a history of stroke or TIA, those who did or did not receive warfarin before entering the trial, and those with low, medium or high risk of stroke at baseline.

## Implications for clinical practice

The efficacy and safety of the new anticoagulant treatments, at least in the clinical setting, suggests that the threshold for starting anticoagulant therapy has been lowered to a stroke rate of ≥0.9% per year.[56,57] The patients in whom the new oral anticoagulant agents are as effective and safe as warfarin, offer other advantages over warfarin, and overcome the limitations of warfarin, are likely to benefit from these new treatments (Box 1 and Table 1). Many patients will prefer to take the new oral anticoagulant treatments over warfarin for several reasons: these drugs are rapidly effective, thereby removing the need for initial treatment with a rapidly acting injectable anticoagulant, which is required with warfarin if the risk of thromboembolism is high; they do not interact with food and most other medications, such as carbamazepine, phenytoin and amiodarone (which could alter the anticoagulant activity in patients taking warfarin); they do not require monitoring; and they have at least an equivalent efficacy to—and a lower risk of intracranial bleeding than—warfarin. Patients with mild or moderate renal impairment who are taking the new anticoagulant drugs need to be closely monitored, however, as renal function might deteriorate with time, leading to increased plasma concentrations of these agents.

**Box 1** | Patient criteria for new oral anticoagulant drugs

Patients who could benefit from the new oral anticoagulants include those who require rapid onset of anticoagulant action; have normal (or mildly impaired) renal function; have a low risk of gastrointestinal bleeding; either have inadequate access to laboratory monitoring or prefer not to be monitored (monitoring effects); can afford the cost of the new oral anticoagulant drugs; decide against warfarin treatment despite adequate education; previously received warfarin and experienced poor control of international normalized ratio (INR) and time in the therapeutic range (<50–55%) owing to genetic polymorphisms for reduced warfarin metabolism (genetic effects); consume food and alcohol that interacts with warfarin (food effects); and receive other medications that interact with warfarin (drug interactions).

Patients who may not benefit from the new oral anticoagulants include those who maintain a stable INR, high time in the therapeutic range, and low bleeding risk with warfarin; have concerns about compliance with frequent dosing of new anticoagulant drugs; are taking P-glycoprotein inhibitors or inducers; are taking cytochrome p450 3A4 inhibitors or inducers; have poor renal function (or have risk of developing renal impairment); have creatinine clearance <30 ml/min; have severe heart failure; might need rapid reversal of anticoagulant effect (antidote); have recurrent dyspepsia (with dabigatran); have a history of gastrointestinal bleeding; decide against taking the new anticoagulant drugs despite adequate education (some patients prefer INR monitoring); and cannot afford the cost of the new oral anticoagulant treatments.

Warfarin remains the treatment of choice for patients with atrial fibrillation who may not benefit from the new anticoagulant drugs, such as those with a creatinine clearance of <30 ml/min, active liver disease or atrial fibrillation due to valvular heart disease (Box 1). Warfarin also remains the treatment of choice for patients who cannot afford the new anticoagulant agents and those who might not comply with the twice-daily dose of dabigatran and apixaban (for example, those who are already taking multiple medications, or are forgetful or lack motivation), because the risks of ischaemic stroke could substantially increase with poor adherence to short-acting drugs. Warfarin will probably remain the preferred treatment for patients who might need rapid reversal of the anticoagulant effect and who potentially have a greater risk of gastrointestinal haemorrhage with the new anticoagulant agents compared with warfarin.

For patients who are already taking warfarin and wish to switch to a new oral anticoagulant drug, warfarin treatment should be stopped and the INR should be monitored daily, before switching drugs. When the INR has fallen below 2, usually 2–3 days after the cessation of warfarin therapy, treatment with one of the new drugs can be started. If patients are also taking aspirin, or other NSAIDs, the risk of bleeding might be increased around twofold. Concurrent use of other antithrombotic agents (such as thienopyridines) is not recommended owing to an increased risk of bleeding.

The anticoagulant effects of new agents are sufficiently predictable that routine monitoring of patients' INR is not required. Calculations of the effects of rivaroxaban and apixaban in prolonging the prothrombin time, and of the effects of dabigatran in prolonging the activated partial thromboplastin time (aPTT) and thrombin time, are highly variable, as these measurements depend on the reagent and laboratory instrument used.[58–62] However, measurement of these effects is desirable to confirm

dose adequacy, assess adherence, detect toxicity or interaction with other drugs, plan timing of urgent surgery or fibrinolytic therapy, help diagnose the cause of bleeding or thrombembolic ischaemic stroke, and reassure patients that the drug 'is working'. Although measurements of drug effects on the prothrombin time, aPTT and thrombin time might detect a possible overdose, they might not enable the detection of a low-intensity anticoagulant effect that could still predispose patients to bleeding. Alternative strategies for assessing the anticoagulant drug effects include evaluation of anti-activated factor X activity (using a chromogenic assay), which exhibits a linear relationship with the plasma concentrations of apixaban and rivaroxaban, and determination of a dilute thrombin time (using the Hemoclot test), which can be calibrated with dabigatran.[63–66]

For patients who present within 4.5 h of acute ischaemic stroke and who are taking any of the new anticoagulant drugs dabigatran, apixaban and rivaroxaban, fibrinolytic therapy with recombinant tissue plasminogen activator (which helps to break down blood clots) should not be performed if the plasma concentrations of anticoagulant drugs are at therapeutic levels or anticoagulation has been achieved.[67] Although the thrombin time is the optimal measure for the direct thrombin and activated factor X inhibitors, its reliability in this context is questionable; thus, other reperfusion strategies, such as mechanical thrombectomy, should be considered.

If bleeding occurs, the first steps are to identify and compress the bleeding site as much as possible, and to stop the anticoagulant therapy, which will rapidly reduce the blood concentrations of anticoagulant agents owing to their short half-life in patients with normal renal function. If bleeding is severe, supportive strategies include transfusion of fresh frozen plasma or fresh whole blood, and fluid replacement to facilitate diuresis and renal excretion of the anticoagulant drug. In cases of non-compressible major haemorrhage such as intracerebral haemorrhage, surgery and rapid reversal of anticoagulation is necessary. However, the new anticoagulant agents do not have antidotes. Dabigatran can be removed by haemodialysis, but this procedure is invasive and burdensome, and about one-third of dabigatran is bound to plasma proteins and cannot be removed by dialysis. Dialysis is not an option for removal of rivaroxaban and apixaban, which are predominantly protein-bound. Nonactivated four-factor prothrombin complex concentrate (PCC), which contains high concentrations of coagulation factors II, VII, IX and X, can be given as a single intravenous fixed dose of 50 U/kg body weight, which quickly normalizes the prothrombin time in patients taking rivaroxaban.[68] Whether PCC stops bleeding is not known. Clinical trials are required to test the effects of PCC on haemostatic response in patients who are taking rivaroxaban and are actively bleeding. Similarly, recombinant activated factor VII (rFVIIa) normalizes the prothrombin time in nonspecific coagulation tests, but whether it is safe and effective in reversing the anticoagulant effect of rivaroxaban, apixaban and dabigatran has not been established. Like PCC, rFVIIa carries a potential risk of arterial thrombosis.[69]

After starting a new anticoagulant treatment, patients should be followed up at 3 months and every 6 months thereafter to verify tolerance, adherence and persistence, and to check renal function, particularly in patients with moderate renal impairment or increased risk of renal impairment (such as the elderly and those with heart failure). Medication adherence and persistence can be optimized through education of patients and relatives of patients, and via regular follow-up or telephone counselling by nurse practitioners, pharmacists and doctors.[70,71]

Given the looming epidemic of fatal and disabling stroke caused by atrial fibrillation owing to an ageing population, the burden of strokes to the community, the suboptimal anticoagulation of a large proportion of patients with atrial fibrillation who are at risk of stroke, and the cost and inconvenience of INR monitoring in patients treated with warfarin, new anticoagulant drugs are likely to be more cost-effective than warfarin. Provided that high-dose dabigatran tablets cost less than US$13.70 per day (warfarin tablets cost US$1–2 per day), dabigatran is more cost-effective than warfarin, particularly for patients with atrial fibrillation who are at high risk of stroke ($CHADS_2$ >3) or haemorrhage who might not have received warfarin, and for those receiving warfarin who cannot maintain a TTR >72%.[72–74]

## Future perspectives

Further novel anticoagulant agents are currently in trials. A large phase III study (ENGAGE-AF TIMI 48) comparing the activated factor X inhibitor edoxaban with warfarin is ongoing.[75] A direct thrombin inhibitor, AZD0837, has shown effective anticoagulant activity and a low rate of bleeding in phase II studies,[76,77] but phase III trials of this agent are awaited.

Future challenges are to develop accurate quantitative measures of the effects of the new anticoagulant drugs and to find safe and effective antidotes to the new anticoagulant drugs that can be administered easily in patients who have major non-compressible haemorrhage or require urgent surgery. Another challenge will be to design trials to directly compare the new anticoagulants with each other and with antiplatelet therapies.[78]

## Conclusions

Several clinical trials have shed light on the efficacy and safety of anticoagulant therapies for patients with ischaemic stroke. The VKA warfarin has been the mainstay of treatment for recurrent strokes in patients with ischaemic stroke of cardiac origin; however, warfarin treatment has limitations including a slow onset of action, interactions with food and other drugs, and adverse effects such as bleeding. New anticoagulant agents have been developed, such as the direct oral thrombin inhibitor dabigatran and the activated coagulation factor X inhibitors rivaroxaban and apixaban, all of which have similar efficacy and safety to warfarin. Despite their rapid onset of action, few drug interactions, and predictable anticoagulant efficacy that does not require INR monitoring, the effects of the new drugs can neither be reliably measured nor reversed in the event of an emergency (for example,

major non-compressible bleeding or urgent surgery). Furthermore, these new drugs cannot be used in patients with severe renal impairment or active liver disease. Research to overcome the limitations of anticoagulant treatments is ongoing, and the results of the clinical trials are promising.

Further research is needed to quantify the net benefits and hazards of the new anticoagulant drugs versus warfarin treatment, using relative measures for ischaemic, haemorrhagic and fatal outcomes (such as disability-adjusted life years); to determine whether the balance between the benefit and the risk changes with a history of stroke; to further characterize the utilization cost, and effect on quality of life of the new anticoagulant agents; and to establish the long-term safety of these new drugs, given that most patients with atrial fibrillation require lifelong oral anticoagulant therapy. One way to achieve these aims could be through a meta-analysis of the data from all major clinical trials and ongoing phase IV surveillance studies of anticoagulant drugs.

**Review criteria**

Articles for this Review were identified using a PubMed search with the following terms: "transient isch(a)emic attack", "isch(a)emic stroke", "antithrombotic drugs", "anticoagulant(s)", "antiplatelet drugs", "aspirin", "clopidogrel", "vitamin K antagonists", "warfarin", "dabigatran", "rivaroxaban", "apixaban", "edoxaban", "stroke", "stroke prevention", "randomized controlled trial(s)", "systematic review", and "meta-analysis". English-language articles published from January 1966 to February 2012 were selected. Additional references were identified from the publication lists of identified papers and by searches of the author's files.


1. Waldo, A. L., Becker, R. C., Tapson, V. F., Colgan, K. J. & NABOR Steering Committee. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. *J. Am. Coll. Cardiol.* **46**, 1729–1736 (2005).
2. Birman-Deych, E., Radford, M. J., Nilasena, D. S. & Gage, B. F. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke* **37**, 1070–1074 (2006).
3. Pengo, V., Pegoraro, C., Cucchini, U. & Iliceto, S. Worldwide management of oral anticoagulant therapy: the ISAM study. *J. Thromb. Thrombolysis* **21**, 73–77 (2006).
4. Nieuwlaat, R. *et al.* Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. *Eur. Heart J.* **27**, 3018–3026 (2006).
5. Hylek, E. M., Evans-Molina, C., Shea, C., Henault, L. E. & Regan, S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* **115**, 2689–2696 (2007).
6. Wan, Y. *et al.* Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ. Cardiovasc. Qual. Outcomes* **1**, 84–91 (2008).
7. Ogilvie, I. M., Newton, N., Welner, S. A., Cowell, W. & Lip, G. Y. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am. J. Med.* **123**, 638–645 (2010).
8. Paciaroni, M., Agnelli, G., Micheli, S. & Caso, V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. *Stroke* **38**, 423–430 (2007).
9. Hankey, G. J. & Eikelboom, J. W. Dabigatran etexilate: a new oral direct thrombin inhibitor. *Circulation* **123**, 1436–1450 (2011).
10. Eriksson, B. I., Quinlan, D. J. & Eikelboom, J. W. Novel oral factor Xa and thrombin inhibitors in the management of thromboembolism. *Annu. Rev. Med.* **62**, 41–57 (2011).
11. Collins, R. & MacMahon, S. Reliable assessment of the effects of treatment on mortality and major morbidity. I: clinical trials. *Lancet* **357**, 373–380 (2001).
12. Turpie, A. G. & Esmon, C. Venous and arterial thrombosis—pathogenesis and the rationale for anticoagulation. *Thromb. Haemost.* **105**, 586–596 (2011).
13. Sandercock, P. A. G., Counsell, C. & Kamal, A. K. Anticoagulants for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* Issue 4. Art. No.: CD000024. http://dx.doi.org/10.1002/14651858.CD000024.pub3.
14. Sandercock, P., Counsell, C. & Tseng. M.–C. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke *Cochrane Database of Systematic Reviews* Issue 3. Art. No.: CD000119. http://dx.doi.org/10.1002/14651858.CD000119.pub3.
15. Wong, K. S. *et al.* Low molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. *Lancet Neurol.* **6**, 407–413 (2007).
16. Wang, Q. S. *et al.* Low-molecular weight heparin versus aspirin for acute ischemic stroke with large artery occlusive disease: subgroup analyses from the Fraxiparin in Stroke Study for the Treatment of Ischemic Stroke (FISS-tris) study. *Stroke* **43**, 346–349 (2012).
17. Sandercock, P. A., Gibson, L. M. & Liu, M. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. *Cochrane Database of Systematic Reviews* Issue 2. Art. No.: CD000248. http://dx.doi.org/10.1002/14651858.CD000248.pub2.
18. Karthikeyan, G. & Eikelboom, J. W. The CHADS2 score for stroke risk stratification in atrial fibrillation—friend or foe? *Thromb. Haemost.* **104**, 45–48 (2010).
19. Lip, G. Y., Nieuwlaat, R., Pisters, R., Lane, D. A. & Crijns, H. J. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest* **137**, 263–272 (2010).
20. Lip, G. Y. *et al.* Bleeding risk assessment and management in atrial fibrillation patients. Executive summary of a position document from the European Heart Rhythm Association (EHRA), endorsed by the European Society of Cardiology (ESC) working group on thrombosis. *Thromb. Haemost.* **106**, 997–1011 (2011).
21. Lindley, R. I. *et al.* Frequency and risk factors for spontaneous hemorrhagic transformation of cerebral infarction. *J. Stroke Cerebrovasc. Dis.* **13**, 235–246 (2004).
22. European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* **342**, 1255–1262 (1993).
23. Saxena, R. & Koudstaal, P. J. Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischaemic attack. *Cochrane Database of Systematic Reviews* Issue 2. Art. No.: CD000185. http://dx.doi.org/10.1002/14651858.CD000185.pub2.
24. Hart, R. G., Pearce, L. A. & Aguilar, M. I. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann. Intern. Med.* **146**, 857–867 (2007).
25. Saxena, R. & Koudstaal, P. J. Anticoagulants versus antiplatelet therapy for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attack. *Cochrane Database of Systematic Reviews* Issue 4. Art. No.: CD000187. http://dx.doi.org/10.1002/14651858.CD000187.pub2.
26. The ACTIVE Writing Group on behalf of the ACTIVE investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* **367**, 1903–1912 (2006).
27. Healey, J. S. *et al.* Risks and benefits of oral anticoagulation compared with clopidogrel plus aspirin in patients with atrial fibrillation according to stroke risk: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-W). *Stroke* **39**, 1482–1486 (2008).
28. Connolly, S. J. *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **361**, 1139–1151 (2009).
29. Connolly, S. J. *et al.* Newly identified events in the RE-LY trial. *N. Engl. J. Med.* **363**, 1875–1876 (2010).
30. Hohnloser, S. H. *et al.* Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Trial. *Circulation* **125**, 669–676 (2012).
31. Uchino, K. & Hernandez, A. V. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch. Intern. Med.* **172**, 397–402 (2012).
32. Diener H. C. *et al.* Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke:

a subgroup analysis of the RE-LY trial. *Lancet Neurol.* **9**, 1157–1163 (2010).
33. Beasley, B. N., Unger, E. F. & Temple, R. Anticoagulant options—why the FDA approved a higher but not a lower dose of dabigatran. *N. Engl. J. Med.* **364**, 1788–1790 (2011).
34. Wann, L. S. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran). A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation* **123**, 1144–1150 (2011).
35. European Heart Rhythm Association *et al.* Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Europace* **12**, 1360–1420 (2010).
36. Cairns, J. A. *et al.* Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can. J. Cardiol.* **27**, 74–90 (2011).
37. Roskell, N. S., Lip, G. Y., Noack, H., Clemens, A. & Plumb, J. M. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. *Thromb. Haemost.* **104**, 1106–1115 (2010).
38. Kubitza, D., Becka, M., Wensing, G., Voith, B. & Zuehlsdorf, M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59–7939—an oral, direct factor Xa inhibitor—after multiple dosing in healthy male subjects. *Eur. J. Clin. Pharmacol.* **61**, 873–880 (2005).
39. Kubitza, D., Becka, M., Roth, A. & Mueck, W. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. *Curr. Med. Res. Opin.* **24**, 2757–2765 (2008).
40. Weinz, C., Schwarz, T., Kubitza, D. Mueck, W. & Lang, D. Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. *Drug Metab. Dispos.* **37**, 1056–1064 (2009).
41. Patel, M. R. *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N. Engl. J. Med.* **365**, 883–891 (2011).
42. Matilde Sanchez, M. & Chen, X. Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat. *Stat. Med.* **25**, 1169–1181 (2006).
43. Piaggio, G. *et al.* Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* **295**, 1152–1160 (2006).
44. Hankey, G. J. *et al.* Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol.* **11**, 315–322 (2012).
45. FDA approves Xarelto® to prevent stroke in people with common type of abnormal heart rhythm. *FDA.gov* [online], http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm278646.htm (2011).
46. Bayer's Xarelto® approved in the EU for the prevention of stroke in patients with AF and in the treatment of DVT. *Bayer.com* [online], http://www.bayer.com/en/news-detail.aspx?newsid=15486 (2011).
47. Carreiro, J. & Ansell, J. Apixaban, an oral direct factor Xa inhibitor: awaiting the verdict. *Expert Opin. Investig Drugs* **17**, 1937–1945 (2008).
48. Wong, P. C. *et al.* Apixaban, an oral, direct and highly selective factor Xa inhibitor: *in vitro*, antithrombotic and antihemostatic studies. *J. Thromb. Haemost.* **6**, 820–829 (2008).
49. Raghavan, N. *et al.* Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab. Dispos.* **37**, 74–81 (2009).
50. Granger, C. B. *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **365**, 981–992 (2011).
51. Connolly, S. J. Apixaban in patients with atrial fibrillation. *N. Engl. J. Med.* **364**, 806–817 (2011).
52. Lawrence, J. *et al.* Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. *Lancet Neurol.* **11**, 225–231 (2012).
53. Fleck, R. A., Rao, L. V., Rapaport, S. I. & Varki, N. Localization of human tissue factor antigen by immunostaining with monospecific, polyclonal anti-human tissue factor antibody. *Thromb. Res.* **59**, 421–437 (1990).
54. Mackman, N. The role of tissue factor and factor VIIa in hemostasis. *Anesth. Analg.* **108**, 1447–1452 (2009).
55. Wallentin, L. *et al.* Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* **376**, 975–983 (2010).
56. Eckman, M. H., Singer, D. E., Rosand, J. & Greenberg, S. M. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ. Cardiovasc. Qual. Outcomes* **4**, 14–21 (2011).
57. Olesen, J. B. *et al.* Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb. Haemost.* **106**, 739–749 (2011).
58. Stangier, J., Rathgen, K., Stähle, H., Gansser, D. & Roth, W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br. J. Clin. Pharmacol.* **64**, 292–303 (2007).
59. Freyburger, G., Macouillard, G., Labrouche, S. & Sztark, F. Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: two observational studies in patients undergoing total hip or total knee replacement. *Thromb. Res.* **127**, 457–465 (2011).
60. Tripodi, A., Chantarangkul, V., Guinet, C. & Samama, M. M. The international normalized ratio calibrated for rivaroxaban has the potential to normalize prothrombin time results for rivaroxaban-treated patients: results of an *in vitro* study. *J. Thromb. Haemost.* **9**, 226–228 (2011).
61. Samama, M. M. *et al.* Assessment of laboratory assays to measure rivaroxaban—an oral, direct factor Xa inhibitor. *Thromb. Haemost.* **103**, 815–825 (2010).
62. Samama, M. M. & Guinet, C. Laboratory assessment of new anticoagulants. *Clin. Chem. Lab. Med.* **49**, 761–772 (2011).
63. Samama, M. M. *et al.* Assessment of laboratory assays to measure rivaroxaban—an oral, direct factor Xa inhibitor. *Thromb. Haemost.* **103**, 815–825 (2010).
64. Samama, M. M., Amiral, J., Guinet, C., Perzborn, E. & Depasse, F. An optimised, rapid chromogenic assay, specific for measuring direct factor Xa inhibitors (rivaroxaban) in plasma. *Thromb. Haemost.* **104**, 1078–1079 (2010).
65. Lindhoff-Last, E., Samama, M. M., Ortel, T. L., Weitz, J. I. & Spiro, T. E. Assays for measuring rivaroxaban: their suitability and limitations. *Ther. Drug Monit.* **32**, 673–679 (2010).
66. Tripodi, A. Measuring the anticoagulant effect of direct factor Xa inhibitors. Is the anti-Xa assay preferable to the prothrombin time test? *Thromb. Haemost.* **105**, 735–736 (2011).
67. Dempfle, C. E. & Hennerici, M. G. Fibrinolytic treatment of acute ischemic stroke for patients on new oral anticoagulant drugs. *Cerebrovasc. Dis.* **32**, 616–619 (2011).
68. Eerenberg, E. S. *et al.* Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. **124**, 1573–1579 (2011).
69. Levi, M., Levy, J. H., Andersen, H. F. & Truloff, D. Safety of recombinant activated factor VII in randomized clinical trials. *N. Engl. J. Med.* **363**, 1791–1800 (2010).
70. Ho, P. M., Bryson, C. L. & Rumsfeld, J. S. Medication adherence: its importance in cardiovascular outcomes. *Circulation* **119**, 3028–3035 (2009).
71. Doggrell, S. A. Adherence to medicines in the older-aged with chronic conditions: does intervention by an allied health professional help? *Drugs Aging* **27**, 239–254 (2010).
72. Freeman, J. V. *et al.* Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann. Intern. Med.* **154**, 1–11 (2011).
73. Shah, S. V. & Gage, B. F. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation* **123**, 2562–2570 (2011).
74. Pink, J., Lane, S., Pirmohamed, M. & Hughes, D. A. Dabigatran etexilate versus warfarin in management of non-valvular atrial fibrillation in UK context: quantitative benefit–harm and economic analyses. *BMJ* **343**, d6333 (2011).
75. Ruff, C. T. *et al.* Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am. Heart J.* **160**, 635–641 (2010).
76. Lip, G. Y. *et al.* Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a phase II study of AZD0837 in patients who are appropriate for but unable or unwilling to take vitamin K antagonist therapy. *Thromb. Res.* **127**, 91–99 (2011).
77. Lip, G. Y. *et al.* Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized dose-guiding, safety, and tolerability study of four doses of AZD0837 vs vitamin K antagonists. *Eur. Heart J.* **30**, 2897–2907 (2009).
78. Hankey, G. J. & Eikelboom, J. W. What do the results of the PRoFESS trial teach us? *Lancet Neurol.* **7**, 860–862 (2008).

**Supplementary information**
Supplementary information is linked to the online version of the paper at www.nature.com/nrneurol