Antithrombotic drugs for patients with ischaemic stroke and transient ischaemic attack to prevent recurrent major vascular events

Graeme J Hankey, John W Eikelboom

Aspirin is widely used for the prevention of recurrent stroke in patients with transient ischaemic attack (TIA) and ischaemic stroke of arterial origin, because it is effective and inexpensive. Clopidogrel and the combination of aspirin and extended-release dipyridamole are more effective than aspirin, but are also much more expensive. No other antithrombotic regimens provide significant advantages over aspirin, although cilostazol and the novel platelet protease activated receptor-1 antagonist, SCH 530348, are currently being evaluated. For patients with TIA and ischaemic stroke of cardiac origin due to atrial fibrillation, vitamin K antagonists (VKAs) are highly effective in preventing recurrent ischaemic stroke but have important limitations and are thus underused. Antiplatelet therapy is much less effective than VKAs. The direct thrombin inhibitor, dabigatran etexilate, has shown efficacy over warfarin in a recent trial. Other new anticoagulants, including the oral factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban, the parenteral factor Xa inhibitor, idrabiotaparinux, and the novel VKA, tecarfarin, are currently being assessed.

Introduction

An important component of the management of patients with a recent transient ischaemic attack (TIA) ischaemic stroke is minimisation of the very high risk of a recurrent stroke in the first 3 months (about 17% [95% CI 14–21%])1 and the continuing long-term risk of recurrent stroke, myocardial infarction, and death due to vascular causes (major vascular events), which is about 44% (95% CI 42–46%) over 10 years.2 Strategies to reduce these risks depend on the underlying cause of the TIA or ischaemic stroke, and include carotid revascularisation, vascular risk factor control, and antithrombotic therapy.

The past year has seen the publication of results of some of the largest clinical trials of antithrombotic therapies to prevent stroke and other major vascular events among patients with TIA and ischaemic stroke. In this Review, we discuss these results in the context of current best evidence and examine how they may affect the prophylactic antithrombotic management of patients with TIA and ischaemic stroke.

Prevention of recurrent ischaemic stroke of arterial origin

For the prevention of recurrent ischaemic stroke of arterial origin, the best antithrombotic regimen is antiplatelet therapy,3 of which aspirin has been the mainstay.4 The increased risk of bleeding is mainly due to an increase in major gastrointestinal bleeding (RR 2.07 [95% CI 1.61–2.66]; absolute annual increase 0.12% [0.07–0.19%]) and intracranial bleeding (RR 1.65 [1.06–5.99]; absolute annual increase 0.12% [0.01–0.08%]).5

The modest treatment effect of aspirin in many patients may be attributable to non-compliance,6 and in some patients to suboptimum platelet inhibition by aspirin, as shown by incomplete inhibition of thromboxane A2 production or of platelet activation and aggregation.7,8 Decreasing response to aspirin is correlated independently with increasing risk of cardiovascular events.7 Potential causes of a reduced response to aspirin include inadequate dose, genetic polymorphisms of PTGS1 (which encodes prostaglandin G/H synthase 1, formerly cyclo-oxygenase 1) and other genes involved in thromboxane biosynthesis, upregulation of non-platelet sources of thromboxane biosynthesis, increased platelet turnover, and drug interactions (eg, with non-steroidal anti-inflammatory drugs [NSAIDs]).9 The specific NSAIDs that may lead to a less than expected inhibition of platelet function by aspirin are ibuprofen, naproxen, and possibly other non-selective NSAIDs, because they compete with aspirin for access to its target (the active site at position 530 of a serine residue in the core of the cyclo-oxygenase enzyme).10–13

Aspirin hyporesponsiveness can potentially be overcome by increasing the dose or frequency of administration, and by avoiding drugs that interact with aspirin. However, the benefit of these measures on clinical outcomes remains unproven.14–15 Established alternatives to aspirin include clopidogrel and the combination of aspirin and extended-release (ER) dipyridamole.

Clopidogrel

Clopidogrel is significantly but marginally more effective than aspirin: it reduced the long-term risk of stroke and...
other major vascular events by 8.7% (95% CI 0.3–16.5%) compared with aspirin among 19,185 patients at high vascular risk, and by 7.3% (−5.7% to 18.7%) among a subgroup of 6431 patients with ischaemic stroke (figure 1). Clopidogrel also causes less gastrointestinal bleeding than 325 mg aspirin daily (RR 0.69 [95% CI 0.48–1.00]; absolute annual decrease 0.12% [0.00–0.28%]), but does not reduce the risk of other types of bleeding. However, the cost of clopidogrel is substantially greater than that of aspirin.

Like aspirin, the response of platelets to clopidogrel treatment also varies, and may be due to clinical, cellular, or genetic factors. Clopidogrel is an inactive prodrug that requires two-step oxidation by the hepatic cytochrome P450 (CYP) system to generate its active compound, the thiol metabolite, which targets and irreversibly inhibits the ADP P2Y purinoceptor 12 on circulating platelets (figure 2). The hepatic CYP isoenzymes involved in this two-step metabolism process of clopidogrel include CYP2C19.

---

**Figure 1: Relative effects of antplatelet regimens versus placebo, aspirin, and clopidogrel in reducing the risk of stroke, myocardial infarction, or vascular death (major vascular events)**

The x-axis shows the degree of reduction in risk of stroke, myocardial infarction, or vascular events/death with each antplatelet regimen. Data derived from table 1. Point estimates and 95% CIs are shown in comparison with placebo (zero), aspirin (13%), or clopidogrel (22%), derived from a systematic review of all trials.5–13

**Table 1: Summary of the results of RCTs of antplatelet drugs in patients with TIA or ischaemic stroke of presumed arterial origin**

<table>
<thead>
<tr>
<th>Drugs compared</th>
<th>Study description</th>
<th>Qualifying diagnosis</th>
<th>Patients (n)</th>
<th>Primary outcome</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin vs control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Algra et al (1999)5</td>
<td>Aspirin vs control</td>
<td>Meta-analysis of 11 RCTs</td>
<td>9469</td>
<td>Stroke, MI, or VD</td>
<td>Risk ratio 0.87 (0.81–0.94)</td>
</tr>
<tr>
<td><strong>Antiplatelet drugs vs aspirin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Schryver et al (2007)6</td>
<td>Dipyridamole vs aspirin</td>
<td>Meta-analysis of 3 RCTs</td>
<td>3386</td>
<td>Stroke, MI, or VD</td>
<td>Risk ratio 1.02 (0.88–1.18)</td>
</tr>
<tr>
<td>Costa et al (2005)7</td>
<td>Triflusal vs aspirin</td>
<td>Meta-analysis of 4 RCTs</td>
<td>2918</td>
<td>Stroke, MI, or VD</td>
<td>Odds ratio 0.98 (0.79–1.20)</td>
</tr>
<tr>
<td>Sudlow et al (2009)1</td>
<td>Ticlopidine vs aspirin</td>
<td>RCT</td>
<td>3069</td>
<td>Stroke, MI, or VD</td>
<td>Odds ratio 0.93 (0.79–1.09)</td>
</tr>
<tr>
<td>CAPRIE Steering Committee (1996)8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>Clopidogrel vs aspirin</td>
<td>RCT</td>
<td>19,185</td>
<td>Ischaemic stroke, MI, or symptomatic PAD</td>
<td>Risk ratio 0.91 (0.83–0.997)</td>
</tr>
<tr>
<td>Subgroup</td>
<td>Clopidogrel vs aspirin</td>
<td>RCT</td>
<td>6431</td>
<td>Ischaemic stroke, MI, or symptomatic PAD</td>
<td>Risk ratio 0.93 (0.82–1.06)</td>
</tr>
<tr>
<td>All patients</td>
<td>Clopidogrel+aspirin vs aspirin</td>
<td>RCT</td>
<td>15,602</td>
<td>Stroke, MI, or VD</td>
<td>Risk ratio 0.93 (0.85–1.05)</td>
</tr>
<tr>
<td>Subgroup</td>
<td>Clopidogrel+aspirin vs aspirin</td>
<td>RCT</td>
<td>4,320</td>
<td>Stroke, MI, or VD</td>
<td>Risk ratio 0.84 (0.69–1.03)</td>
</tr>
<tr>
<td>Halkes et al (2008)10</td>
<td>Dipyridamole+aspirin vs aspirin</td>
<td>Meta-analysis of 6 RCTs</td>
<td>7,612</td>
<td>Stroke, MI, or VD</td>
<td>Hazard ratio 0.82 (0.72–0.92)</td>
</tr>
<tr>
<td><strong>Antiplatelet drugs vs clopidogrel</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diener et al (2005)11</td>
<td>Clopidogrel+aspirin vs clopidogrel</td>
<td>RCT</td>
<td>7,599</td>
<td>Ischaemic stroke, MI, VD or rehospitalisation for acute ischaemia</td>
<td>Risk ratio 0.94 (0.84–1.05)</td>
</tr>
<tr>
<td>Sacco et al (2008)12</td>
<td>Dipyridamole+aspirin vs clopidogrel</td>
<td>RCT</td>
<td>20,322</td>
<td>Stroke, MI, or VD</td>
<td>Hazard ratio 0.99 (0.92–1.07)</td>
</tr>
</tbody>
</table>

MI=myocardial infarction. PAD=peripheral artery disease. RCT=randomised controlled trial. TIA=transient ischaemic attack of the brain or eye. VD=vascular death.
CYP3A4/5, CYP1A2, CYP2B6, and CYP2C9. Several genetic polymorphisms have been described that may be associated with impaired pharmacokinetic and pharmacodynamic response to clopidogrel, with possible clinical consequences.\textsuperscript{21-23} The first genome-wide association study of clopidogrel response has recently reported that the loss-of-function CYP2C19*2 genotype was associated with diminished effect of clopidogrel inhibition of ADP-induced platelet aggregation and poorer cardiovascular outcomes.\textsuperscript{24} Whether the CYP2C19*2 polymorphism is associated with higher cardiovascular risks that are independent from the diminished conversion of the prodrug to the active form of clopidogrel remains to be determined. Thus a genomic profile may identify patients at risk of ischaemic events while taking clopidogrel and for whom an alternative antiplatelet approach may be more effective. This hypothesis remains to be validated externally.

Concomitant administration of clopidogrel with a proton-pump inhibitor, particularly omeprazole, to minimise the risk of gastrointestinal bleeding complications, also attenuates clopidogrel’s antiplatelet action in about a third of patients.\textsuperscript{25–27} The mechanism is thought to be a drug–drug interaction at the level of the hepatic CYP system, because hepatic metabolisation of omeprazole is also CYP dependent. However, although treatment with a proton-pump inhibitor attenuates the pharmacodynamic effects of clopidogrel, the effect is modest and apparently insufficient to affect the clinical outcome of patients on clopidogrel (or prasugrel)—another thienopyridine.\textsuperscript{28,29}

The long-term use (18 months) of aspirin plus clopidogrel is no more effective than clopidogrel alone in prevention of ischaemic stroke, myocardial infarction, vascular death, and rehospitalisation for acute ischaemia (RR 0·94 [95% CI 0·88–1·00]).\textsuperscript{13} Moreover, use of this combination for 18 months was associated with an increase in life-threatening bleeding (2·6% on aspirin and clopidogrel vs 1·3% on aspirin; absolute risk increase 1·3% [0·6–1·9]).\textsuperscript{12}

**Aspirin plus extended-release dipyridamole**

The combination of aspirin and ER dipyridamole is significantly more effective than aspirin alone in reducing the risk of stroke and other major vascular events (hazard ratio [HR] 0·82 [95% CI 0·72–0·92]), without excessive bleeding or myocardial infarction in patients with previous TIA or ischaemic stroke (figure 1).\textsuperscript{11} However, a direct comparison of 75 mg clopidogrel daily with the combination of 25 mg aspirin and 200 mg ER dipyridamole twice daily in 20 332 patients with ischaemic stroke showed no significant difference between either regimen in the prevention of recurrent stroke (9·0% on aspirin plus ER dipyridamole vs 8·8% on clopidogrel; HR 1·01 [95% CI 0·92–1·11]), myocardial infarction (1·7% vs 1·9%; HR 0·90 [0·73–1·10]), and the composite of stroke, myocardial infarction, and death from vascular causes (13·1% vs 13·1%; HR 0·99 [0·92–1·07]; figure 1).\textsuperscript{13}

Dipyridamole causes headache in 24–70% of patients, which is sufficient to prompt discontinuation in about 10% of patients, usually within the first 3 months.\textsuperscript{16} Headache is more likely to occur in women, non-smokers, and patients with an absence of relevant ischaemic lesions on brain imaging.\textsuperscript{17} The combination of 25 mg aspirin with 200 mg ER dipyridamole costs substantially more than aspirin but less than clopidogrel.

In the USA, use of clopidogrel and the combination of aspirin and ER dipyridamole increased between 2001 and 2005, as their superior efficacy to aspirin was recognised, despite the greater costs of the drugs.\textsuperscript{20}

**Other antithrombotic regimens**

In the acute phase of ischaemic stroke, short-term abciximab is not more effective than aspirin (odds ratio 0·97 [95% CI 0·70–1·36]).\textsuperscript{22} In the longer term, neither oral anticoagulation (HR 1·02 [0·77–1·35]),\textsuperscript{3,34} dipyridamole (RR 1·02 [0·88–1·18]),\textsuperscript{4} triflusal (odds ratio [OR] 0·98 [0·79–1·20]),\textsuperscript{5} the combination of aspirin and clopidogrel (RR 0·93 [0·85–1·05]),\textsuperscript{6} nor terutroban (a specific antagonist of the thromboxane A\textsubscript{2} receptor on platelets and the vessel wall)\textsuperscript{7} have been shown to be more effective than aspirin in the prevention of recurrent stroke and other major vascular events. The trial comparing terutroban with 100 mg aspirin daily in 18 000 patients with a history of recent ischaemic stroke or TIA has recently been halted because interim analyses suggested that continuation of the study would be futile.\textsuperscript{15}

**Promising future antithrombotic regimens**

In acute TIA and ischaemic stroke, the combination of aspirin plus clopidogrel may be more effective than aspirin alone if administered immediately and for only the first
few months, when the risk of recurrent stroke is highest, thus not exposing the patient to the long-term risks of bleeding associated with the combination of clopidogrel and aspirin compared with aspirin or clopidogrel alone.\textsuperscript{10,11} Large phase 3 trials, such as the POINT (Platelet-Oriented Inhibition in New TIA) trial,\textsuperscript{59} are being planned to establish the relative safety and efficacy of the combination of clopidogrel and aspirin compared with aspirin in patients with acute TIA and mild ischaemic stroke. Other antithrombotic agents that have shown efficacy in acute coronary syndromes, such as the newer and more potent thienopyridine, prasugrel,\textsuperscript{18} the non-thienopyridine, ticagrelor (a reversible ADP receptor antagonist),\textsuperscript{19} and the oral factor Xa inhibitors, rivaroxaban and apixaban,\textsuperscript{20,21} may be promising potential treatments for acute TIA and ischaemic stroke, but the expected increase in bleeding associated with these drugs may preclude their further development in acute cerebrovascular disease.

For longer term secondary prevention, cilostazol reduced the risk of stroke by about 39% (95% CI 9–59%) compared with placebo among 1095 Japanese patients with ischaemic stroke,\textsuperscript{42} and by about 38% (–26% to 70%) compared with aspirin in a pilot trial involving 720 Chinese patients with ischaemic stroke.\textsuperscript{43} Larger phase 3 trials are awaited.

SCH 530488 bisulfate is an orally active antagonist of protease-activated receptor 1 (the main thrombin receptor on the surface of platelets), which attenuates thrombin-stimulated platelet aggregation. This drug is currently being compared with placebo for the prevention of myocardial infarction and stroke in 25000 patients with atherosclerosis.\textsuperscript{44}

**Implications for clinicians**

The most important priority in the thromboprophylactic management of patients with ischaemic stroke and TIA of arterial origin is to ensure that they are prescribed, taking, and tolerating an effective antiplatelet drug such as aspirin, clopidogrel, or the combination of aspirin and ER dipyridamole. Because aspirin is widely available, affordable, and effective (albeit modestly), it is arguably the first-line treatment of choice. However, if patients are intolerant of or allergic to aspirin, at high risk of a recurrent stroke (more than 15–20% per year),\textsuperscript{8,9} or have experienced a recurrent ischaemic event of arterial origin while taking aspirin, then one of the two more effective, although more expensive, regimens is indicated.

The decision to start clopidogrel or the combination of aspirin and ER dipyridamole will be determined by several factors: atherothrombotic vascular disease in other vascular beds (aspirin with ER dipyridamole has not been proven to be effective for the treatment of patients with coronary artery disease, but was not associated with any excess myocardial infarction as an outcome event in stroke patients;\textsuperscript{11,13}) a predisposition to adverse effects (eg, major bleeding in 4.1% of patients on aspirin with ER dipyridamole vs 3.6% on clopidogrel; headache in 6% of patients on aspirin with ER dipyridamole vs 1% on clopidogrel); compliance (aspirin with ER dipyridamole is taken twice daily, whereas clopidogrel is taken once daily); patient preference; and affordability.\textsuperscript{15}

**Prevention of recurrent ischaemic stroke of cardiac origin**

For patients with TIA or ischaemic stroke due to thromboembolism from the heart, particularly those with atrial fibrillation (AF), the use of oral anticoagulation with vitamin K antagonists (VKAs; ie, warfarin) to maintain an international normalised ratio (INR) of 2.0–3.0, has been the cornerstone of antithrombotic therapy for more than 20 years.\textsuperscript{45,46}

**Warfarin**

Warfarin reduces the risk of recurrent stroke or systemic embolism by about 61% (95% CI 37–75%) compared with control in AF patients with recent TIA or ischaemic stroke.\textsuperscript{47} This proportional risk reduction is consistent with that observed for the prevention of first-ever stroke among individuals with AF, including the elderly (figure 3).\textsuperscript{47,49} Warfarin also increases the odds of major extracranial haemorrhage (OR 4.3 [95% CI 1.5–12.1]).\textsuperscript{49}

The decision to prescribe warfarin, and the net clinical benefit of warfarin, is based on an accurate assessment of the likely absolute annual risk of stroke without warfarin, and whether the likely benefits of warfarin (a two-thirds reduction in absolute stroke risk) are likely to outweigh the risks of bleeding associated with warfarin use.\textsuperscript{33} The threshold stroke rate for which warfarin prophylaxis is indicated is more than 2% per year (provided the risk of life-threatening or intracranial bleeding with warfarin is predicted to be less than 1% per year).

Pooled estimates from systematic reviews of AF patients enrolled in observational studies and clinical trials indicate that the most important, significant, independent risk factors for stroke in patients with AF seem to be prior stroke or TIA (RR 2.5 [95% CI 1.9–3.3]), advancing age (RR 1.4 [1.3–1.6] per decade), history of hypertension (RR 1.9 [1.5–2.4]), systolic blood pressure

---

**Figure 3: Indirect comparisons of the relative effects of placebo or no therapy, antiplatelet regimens (aspirin and clopidogrel, and aspirin alone), and anticoagulant regimens (ximelagatran and dabigatran), when compared with warfarin, in reducing the risk of stroke and systemic embolism among patients with atrial fibrillation in clinical trials**

Effect estimates and 95% CIs are shown (log scale). Estimates calculated by Mantel-Haenszel method and random-effects models.
The most important function of the schemes is to identify patients with AF who are likely to benefit from warfarin, and thus accurately discriminate patients at high risk of stroke or systemic embolism (for whom warfarin is indicated) from those at moderate risk (warfarin or aspirin) and low risk (aspirin). Although the CHADS₂ score might be categorised as moderate risk, antithrombotic therapy with either VKA or aspirin is reasonable depending on bleeding risks, ability to safely sustain anticoagulation, and patient preferences. No clear whether history of heart failure, recent heart failure, or current heart failure. Prior stroke, TIA, or systemic embolism. Echocardiographic parameters not specifically defined. TIA=transient ischaemic attack. VKA= vitamin K antagonist.

Table 2: Schemes of stratifying risk of stroke among patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Low risk</th>
<th>Moderate risk</th>
<th>High risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS₂</td>
<td>0 points</td>
<td>1 point*</td>
<td>≥2 points</td>
<td>1 point each for congestive heart failure, hypertension, age &gt;75 years, diabetes; 2 points for stroke or TIA</td>
</tr>
<tr>
<td>American College of Cardiology, American Heart Association, and European Society of Cardiology guidelines</td>
<td>No moderate or high risk factors§</td>
<td>Age ≥75 years, heart failure, hypertension, diabetes; left ventricular ejection fraction &lt;35% or fractional shortening &lt;25%</td>
<td>Prior thromboembolism</td>
<td></td>
</tr>
<tr>
<td>American College of Chest Physicians practice guidelines</td>
<td>No moderate or high risk factors§</td>
<td>Age ≥75 years, heart failure, history of hypertension, diabetes; moderately to severely impaired left ventricular systolic function**</td>
<td>Prior thromboembolism</td>
<td></td>
</tr>
</tbody>
</table>

*In previous studies, moderate risk was typically defined as CHADS₂ scores of 1 or 2; the current definition makes the three schemes very similar. Recent heart failure exacerbation was used in the original stratification, although this has now been replaced by any prior or current heart failure. †History of hypertension, not specifically defined. ‡Less well-validated risk factors were female sex, coronary artery disease, and age 65–74 years. It is unclear whether patients with at least one of these factors should be categorised as moderate risk. Antithrombotic therapy with either VKA or aspirin is reasonable depending on bleeding risks, ability to safely sustain anticoagulation, and patient preferences. ¶Not clear whether history of heart failure, recent heart failure, or current heart failure. §§Prior stroke, TIA, or systemic embolism. ¶¶Echocardiographic parameters not specifically defined. TIA=transient ischaemic attack. VKA= vitamin K antagonist.

above 160 mm Hg (RR 1.4 [1.2–1.6] for a 30 mm Hg difference), and diabetes (RR 1.7 [1.5–2.1]).

More than a dozen models for calculating stroke risk have been published, based on many of the important risk factors mentioned above. Three commonly accepted schemes of stratifying risk of stroke among patients with paroxysmal and permanent AF are shown in table 2. The most popular is the CHADS₂ scoring system, which assigns one point for each of congestive heart failure, hypertension, age older than 75 years, and diabetes mellitus, and two points for prior stroke or TIA. A CHADS₂ score of 1 carries an ischaemic stroke risk of about 2% per year. The other two schemes add echocardiographic evidence of left ventricular systolic dysfunction to the CHADS₂ variables. This addition shifts about 5% of patients with AF into a higher risk stratum.

The most important function of the schemes is to identify patients with AF who are likely to benefit from warfarin, and thus accurately discriminate patients at high risk of stroke or systemic embolism (for whom warfarin is indicated) from those at moderate risk (warfarin or aspirin) and low risk (aspirin). Although the CHADS₂ score might not be as accurate as the other schemes in predicting stroke risk, its discriminative capacity is sufficiently adequate to guide thromboprophylactic treatment decisions, and it can be calculated at the bedside or in the clinic from simple clinical features (without requiring access to echocardiography).

However, several caveats remain about these schemes, which require further research. First, how heart failure contributes to the risk stratification schemes, given that it is not an independent significant predictor of stroke in AF, is uncertain (see above). Second, the absolute stroke rates associated with a classification of high risk are imprecise owing to small numbers of patients studied. Third, other factors that were not measured or included in the initial prognostic studies have been shown to improve stroke risk prediction (eg, markers of a prothrombotic state contributing to left atrial appendage thrombus formation), but whether they significantly improve discriminative ability and thereby influence thromboprophylactic treatment decisions remains uncertain. Fourth, when tested in a large administrative outpatient database in which overall stroke rates were low, the schemes did not perform so well (all schemes had only fair discriminating ability in the prediction of thromboembolic events). Fifth, whether the treatment of any of the modifiable independent predictors (eg, heart failure, hypertension, diabetes) reduces strokes in patients with AF is uncertain, although there is a suggestion that lowering blood pressure is effective. Finally, the effect of warfarin treatment on the prediction models is uncertain. A hypothesis-generating post-hoc analysis of the SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation) trials suggests that, among patients with AF who take warfarin, independent risk factors for stroke include prior stroke or TIA, higher systolic blood pressure, higher (within-patient) variability in the INR, lower proportion of prevalent warfarin use, lower proportion of statin use, and lower plasma concentrations of high-density lipoprotein.
fixed-dose approach is commonly used. However, adverse effects can arise while finding the appropriate maintenance dose, which can vary by a factor of ten among patients. This dose variability is determined by clinical factors, demographics, and variations in two genes: CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1).

An algorithm for estimating the appropriate warfarin dose that is based on clinical and genetic data has been developed and validated, and provided significantly better predictions of appropriate dose of warfarin than either the clinical algorithm or a fixed-dose approach. This suggests that testing for variants in genes involved in warfarin metabolism and sensitivity (CYP2C9*2, CYP2C9*3, and/or VKORC1) might allow more personalised dosing of warfarin during the induction phase than would standard warfarin induction. However, in terms of fewer future strokes or bleeds, any clinical benefits of genotyping are unproven, and the additional cost of genotype testing (about US$400 per person) is unlikely to be cost-effective for typical patients with non-valvular AF, yielding a gain of 0.003 quality-adjusted life-years (QALYs), which equates to about 1 day more over the lifetime of the patient; the incremental cost-effectiveness ratio is about $170,000 per QALY gained. Thus, there is only a 10% chance that genotype-guided dosing is likely to be cost-effective (ie, <US$50,000 per QALY). For genetic testing to be cost-effective and cost less than US$50,000 per QALY, it would have to be restricted to patients at high risk for haemorrhage or meet the following optimistic criteria: prevent more than 32% of major bleeding events, be available within 24 h, and cost less than US$200.63

Aspirin and clopidogrel versus warfarin

The combination of aspirin and clopidogrel is not as effective as warfarin, particularly for patients who are taking warfarin without complication. Among 6706 patients with AF, random assignment to clopidogrel (75 mg once daily) plus aspirin resulted in a 50% reduction in vascular events compared with those on clopidogrel plus aspirin vs aspirin alone (5.6% per year for those on clopidogrel plus aspirin vs 3.9% per year on warfarin; RR 1.10 [95% CI 1.02–1.20]; figure 3). There was no significant difference in major bleeding between the two treatment groups (2.4% per year for those on clopidogrel plus aspirin vs 2.2% per year on warfarin; RR 1.10 [0.83–1.45]).

A subgroup analysis of the results of this trial raised the hypothesis that most of the benefit of warfarin over the combination of aspirin and clopidogrel was in patients who were already taking and tolerating oral anticoagulant therapy (ie, had survived the warfarin stress test), compared with patients who were warfarin naive and about to start warfarin. Patients who were already taking warfarin at study entry and were randomly assigned to continue oral anticoagulation therapy had a substantial reduction in vascular events compared with those on the combination of clopidogrel and aspirin (3.7% vs 5.5% per year; RR 0.67 [95% CI 0.55–0.84]) and a significantly lower risk of major bleeding (2.0% vs 2.6% per year; RR 0.77 [0.56–1.06]). By contrast, patients who were not taking oral anticoagulants at study entry (ie, those who were warfarin naive) and were randomly assigned to start oral anticoagulation had a similar rate of vascular events (4.7% vs 5.9% per year; RR 0.79 [0.53–1.18]) and a higher
risk of major bleeding (2·9% vs 1·7% per year; RR 1·69 [0·93–3·12]) compared with those on the combination of clopidogrel and aspirin. Another subgroup analyses showed that patients with paroxysmal AF who were treated with aspirin plus clopidogrel or oral anticoagulation had a similar risk for thromboembolic events and similar reduction in risk of stroke with oral anticoagulation therapy as patients with sustained AF. However, for patients who were enrolled at centres where time in the therapeutic range was less than the median for the trial, warfarin had no advantage over the combination of aspirin and clopidogrel.

**Aspirin and clopidogrel versus aspirin alone**

Among 7554 patients with AF for whom VKA therapy was considered unsuitable (physician’s judgment that VKA was inappropriate, 50%; specific risk of bleeding, 23%; patient’s preference not to take VKA, 27%), random assignment to 75 mg clopidogrel once daily plus aspirin was associated with a reduction in the primary outcome of stroke, myocardial infarction, non-CNS systemic embolism, or death from vascular causes, after a median of 3·6 years of follow-up, compared with placebo plus aspirin (6·8% vs 7·6% per year; RR 0·89 [95% CI 0·81–0·98]). However, major bleeding was greater among patients assigned clopidogrel plus aspirin versus those on aspirin alone (2·0% vs 1·3% per year; RR 1·57 [1·29–1·92]). These data suggest that treating 1000 patients with AF for 1 year with clopidogrel plus aspirin prevents eight major vascular events (including two fatal and three disabling strokes) and causes seven major haemorrhages (one fatal) compared with aspirin alone. However, it is not yet known how to reliably identify the few patients who will benefit and the very few who will be harmed by use of aspirin and clopidogrel compared with aspirin alone.

**Aspirin and warfarin**

Because patients with AF often have coexisting atherosclerotic vascular disease (ischaemic heart disease is a common cause of AF), both warfarin and aspirin are considered to be needed to prevent thrombus formation in the left atrium and arteries. Warfarin prevents the formation of fibrin-rich thrombus (so-called “red clot”) associated with AF, whereas antiplatelet treatment prevents the formation of the platelet-rich thrombus (so-called “white clot”) associated with arterial vascular disease. This principle applies particularly to patients with AF who present with unstable vascular disease manifest by an acute coronary syndrome, or who are undergoing vascular injury by means of percutaneous coronary or carotid intervention or stenting, for which aspirin plus clopidogrel is recommended. For such patients with AF, the long-term benefit-to-harm ratio of combination therapy is not known and should be left to the clinician’s discretion. However, for patients with AF who have stable vascular disease, there is no reliable evidence to indicate that adding aspirin (or clopidogrel) to warfarin is safe and effective compared with warfarin alone. Indeed, warfarin can be an effective drug for stable coronary and cerebrovascular disease, and the haemorrhage rate seems to be greater with the combination of aspirin and warfarin.

**Direct thrombin inhibitors**

The direct thrombin inhibitor, ximelagatran, is similar to warfarin in efficacy and safety but is hepatotoxic. Among 7329 patients with AF who were randomly assigned to warfarin (INR 2·0–3·0) or ximelagatran (36 mg twice daily) and followed for 11 346 patient-years (mean 18·5 months per patient), ximelagatran was considered not inferior to warfarin in prevention of stroke and systemic embolism (1·62% vs 1·65% per year; p=0·94) or in causing major bleeding (1·88% vs 2·46% per year; p=0·054). However, assignment to ximelagatran was associated with a significant increase in the number of patients in whom a liver enzyme rose more than three times the upper limit of normal compared with warfarin (6·1% vs 0·8%; p<0·0001). Although usually reversible, this precluded the further development of ximelagatran in AF.

**Factor Xa inhibitors**

Idraparinux is a synthetic analogue of the heparin pentasaccharide that binds irreversibly to antithrombin and induces a conformational change that leads to inactivation of activated factor X. Idraparinux has a half-life of 80–130 h and is given by subcutaneous injection once weekly. Subcutaneous idraparinux may be more effective than warfarin; however, in the doses and patients studied, it was associated with substantially higher bleeding rates than warfarin. Among 4576 patients with AF who were randomly assigned to subcutaneous

<table>
<thead>
<tr>
<th>Target</th>
<th>Dosing</th>
<th>Prodrug</th>
<th>Bioavailability</th>
<th>Coagulation monitoring</th>
<th>Half-life (h)</th>
<th>Renal clearance</th>
<th>Drug interactions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran etexilate</td>
<td>Thrombin, Fixed, twice daily</td>
<td>Yes</td>
<td>6%</td>
<td>No</td>
<td>12–17</td>
<td>80%</td>
<td>P-glycoprotein inhibitors</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Factor Xa, Fixed, once daily</td>
<td>No</td>
<td>80%</td>
<td>No</td>
<td>5–9</td>
<td>65%</td>
<td>Potent inhibitors of CYP3A4 and P-glycoprotein</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Factor Xa, Fixed, once daily</td>
<td>No</td>
<td>50%</td>
<td>No</td>
<td>12</td>
<td>25%</td>
<td>Potent inhibitors of CYP3A4</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Factor Xa, Fixed, once daily</td>
<td>No</td>
<td>50%</td>
<td>No</td>
<td>9–11</td>
<td>25%</td>
<td>Potent inhibitors of CYP3A4 and P-glycoprotein</td>
</tr>
</tbody>
</table>

*P-glycoprotein inhibitors: amiodarone, verapamil, clarithromycin, quinidine. Quinidine is contraindicated in patients receiving dabigatran etexilate. CYP3A4 inhibitors: ketoconazole, macrolide antibiotics (eg, clarithromycin), and protease inhibitors (eg, atazanavir). CYP3A4=cytochrome P450 isoenzyme 3A4.

Table 3: Pharmacological characteristics of new oral anticoagulants under assessment for the prevention of cardioembolic stroke.
idraparinux (2.5 mg weekly) or adjusted-dose VKA (target INR 2.0–3.0), the trial was stopped after a mean follow-up of 11 months because of excess clinically relevant bleeding among patients assigned idraparinux compared with VKA (19.7 vs 11.3 events per 100 patient-years; HR 1.74 [95% CI 1.47–2.06]). Elderly patients and those with renal impairment were at greater risk of such complications. There was no significant difference in the rate of the primary outcome of stroke and systemic embolism (0.9 vs 1.3 events per 100 patient-years; HR 0.71 [0.39–1.30]; p=0.007 for non-inferiority) or deaths (3.2 vs 2.9 deaths per 100 patient-years; p=0.49) between patients on idraparinux versus those receiving VKA.46

Promising future anticoagulants

*Oral direct thrombin inhibitors*

Dabigatran etexilate is a prodrug that is given orally in a fixed dose and rapidly converted by CYP-independent esterases to dabigatran, a potent reversible direct competitive inhibitor of thrombin with a rapid onset of action, predictable and consistent anticoagulant effect, and half-life of 12–17 h (table 3, figure 4).9 The RE-LY (Randomised Evaluation of Long-term anticoagulant therapY) trial was a phase 3, multicentre, prospective, open-label, randomised trial with blinded assessment of all outcomes that aimed to determine whether at least one dose of dabigatran etexilate would be non-inferior to warfarin.26 18 113 patients with non-valvular AF and at least one risk factor for stroke were randomly assigned to receive fixed (masked) doses of dabigatran (110 mg or 150 mg twice daily) or open-label, adjusted-dose warfarin (INR 2.0–3.0). After a median follow-up of 2 years, the rates of systemic embolism or stroke (including haemorrhagic stroke) were similar among patients assigned 110 mg dabigatran (1.53% per year) and warfarin (1.69% per year; HR 0.91 [95% CI 0.74–1.11]; p<0.001 for non-inferiority) and significantly lower among patients assigned dabigatran 150 mg twice daily (1.11% per year; HR 0.66 [0.53–0.82]; figures 3 and 5).27

Compared with warfarin (3.36% per year), the annual rate of major bleeding was lower among patients assigned 110 mg dabigatran (2.71% per year; RR 0.80 [95% CI 0.69–0.93]) and similar among patients assigned 150 mg dabigatran (3.11% per year; RR 0.93 [0.81–1.07]). However, gastrointestinal bleeding was significantly increased in those on dabigatran etexilate compared with patients on warfarin. Compared with warfarin (0.38% per year), rates of haemorrhagic stroke were lower with 110 mg dabigatran (0.12% per year; RR 0.31 [0.17–0.56]) and 150 mg dabigatran (0.10% per year; RR 0.26 [0.14–0.49]).28

Rates of myocardial infarction were significantly more common with dabigatran (0.72% and 0.74% with 110 mg and 150 mg, respectively) than with warfarin (0.53%), although the mechanism remains unascertained. Rates of dyspepsia (including abdominal pain) were increased with dabigatran (11.8% with 110 mg, 11.3% with 150 mg) compared with warfarin (5.8%), presumably because of the tartaric acid content of the dabigatran etexilate capsule. This contributed to the greater dropout rate over 2 years with dabigatran (about 21%) than with warfarin (16–66%). Combined net clinical benefit outcomes (major vascular events, major bleeding, and death) were 7.64% per year with warfarin compared to 7.09% per year with 110 mg dabigatran (RR 0.92 [95% CI 0.84–1.02]; p=0.10) and 6.91% per year with 150 mg dabigatran (RR 0.91 [95% CI 0.82–1.00]; p=0.04).29

The validity of these results might be questioned because the administration of warfarin was not blinded, raising the possibility that patterns of reporting outcome and adverse events by patients assigned warfarin and their clinicians could have been systematically different from patients assigned dabigatran. However, such potential bias is likely to have been reduced because all hospital records were reviewed to facilitate complete...
ascertainment of events, and all events were adjudicated by two investigators who were independent and blinded to the treatment allocation. Furthermore, allocation of the dabigatran doses was blinded and efficacy results were internally consistent by dose. Other factors that suggest that ascertainment of outcome events was not biased include the unexpected excess of myocardial infarction in patients treated with dabigatran, the higher gastrointestinal bleeding rates with the higher dose (150 mg) of dabigatran, and the significant reduction in cardiovascular death and the borderline significant (p=0·051) reduction in total mortality among patients assigned the higher dose of dabigatran. Among patients assigned warfarin, the time in the therapeutic range, excluding the first week of therapy, averaged 64% (67% experienced, 61% naive), indicating a similar quality of warfarin management to that achieved in contemporary trials.48,50,51 Only 20 (0·1%) patients were lost to follow-up. The results are therefore likely to be internally valid.

The results are also likely to be generalisable to similar patients to those enrolled from the 951 centres and 44 countries in RE-LY.49 These patients were of average age 71 years, two-thirds were men, a fifth had a prior stroke or TIA, a third had a CHADS2 score of 3 or more, and 50% were naive to previous oral anticoagulation (ie, so-called anticoagulation “starters”).51 However, the results of RE-LY cannot be generalised to patients with liver disease or a creatinine clearance of less than 30 mL/min. In addition, the potential benefits of dabigatran compared with warfarin may be reduced in poorly compliant patients (because the longer half-life of warfarin could provide them with a more consistent anticoagulant effect) and in patients taking potent P-glycoprotein inhibitors (table 3), which can increase serum concentrations of dabigatran.

Several general concerns remain: (1) the potential safety and use of the lower dose (110 mg) in small, older patients with moderate renal impairment; (2) the safety and efficacy of dabigatran in the long term (ie, >2 years mean follow-up), which is currently being assessed in an follow-up study of RE-LY patients;50 (3) the implications, if any, of there being no antidote to dabigatran (although dabigatran can be eliminated by means of dialysis); and (4) the cost. Given the looming epidemic of fatal and disabling stroke caused by AF (as the population ages), the enormous cost of these strokes to the community, the suboptimum anticoagulation of a large proportion of the AF population, and the cost and inconvenience of INR monitoring among those prescribed warfarin, it is likely that the incremental cost-effectiveness of dabigatran versus warfarin will be favourable, even if the cost of dabigatran tablets is substantially greater than that of warfarin.

A specific question for stroke clinicians is whether the overall results of RE-LY can be generalised to patients with AF and a history of stroke or TIA. Among the 3623 (20%) patients with a previous stroke or TIA who were enrolled, the results were consistent with the overall trial results (annual rate of the primary outcome event: warfarin, 2.75%; 110 mg dabigatran, 2.32%; 150 mg dabigatran, 2.07%), and there were no significant differences between the HRs for patients with or without a history of cerebral ischaemia (p=0·34 for interaction). However, the 95% CIs for patients with a history of cerebral ischaemia were wide, indicating that evidence for the efficacy of dabigatran compared with warfarin in patients with a history of cerebral ischaemia is still limited.

Dabigatran might be a safe and effective alternative to warfarin for patients with AF at risk of stroke. If, and once, the drug is approved, clinicians are likely to have a choice of doses, which they can tailor to the patient’s risks of stroke and bleeding; the more efficacious 150 mg dose is likely to be appropriate for patients at high risk of stroke, and the safer 110 mg dose for those at high risk of bleeding or drug interactions, such as those taking potent P-glycoprotein inhibitors. However, patients who are already taking and tolerating once-daily warfarin with good INR control may prefer to stay on warfarin and not switch to dabigatran. Despite the potential benefits of dabigatran in lowering rates of stroke and intracerebral haemorrhage and not requiring coagulation monitoring, these patients may be discouraged from a switch because

<table>
<thead>
<tr>
<th>Design</th>
<th>Study size (n)</th>
<th>Patients Interventions</th>
<th>Outcome</th>
<th>Results expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET-AF50</td>
<td>14,266</td>
<td>AF plus ≥2 risk factors for stroke</td>
<td>Rivaroxaban 20 mg daily plus warfarin placebo vs warfarin (INR 2.0–3.0) plus rivaroxaban placebo</td>
<td>Stroke or non-CNS embolism Clinically relevant bleeding 2010</td>
</tr>
<tr>
<td>ARISTOTLE51</td>
<td>15,000</td>
<td>AF plus ≥1 risk factor for stroke</td>
<td>Apixaban 5 mg twice daily plus warfarin placebo vs warfarin (INR 2.0–3.0) plus apixaban placebo twice daily</td>
<td>Stroke or non-CNS embolism Clinically relevant bleeding 2010</td>
</tr>
<tr>
<td>AVERROES52</td>
<td>5,600</td>
<td>AF plus ≥1 risk factor for stroke, 40% warfarin naive</td>
<td>Apixaban 5 mg twice daily vs aspirin</td>
<td>Stroke or non-CNS embolism Clinically relevant bleeding 2010</td>
</tr>
<tr>
<td>ENGAGE-AF TIMI-48</td>
<td>16,500</td>
<td>AF plus ≥1 risk factor for stroke</td>
<td>Edoxaban plus warfarin placebo vs warfarin (INR 2.0–3.0) plus edoxaban placebo</td>
<td>Stroke or non-CNS embolism Clinically relevant bleeding 2012</td>
</tr>
<tr>
<td>BOREALIS53</td>
<td>9,500</td>
<td>AF plus ≥1 risk factor for stroke</td>
<td>Idarabiotaparinux subcutaneously weekly plus warfarin placebo vs warfarin (INR 2.0–3.0) plus idarabiotaparinux placebo*</td>
<td>Stroke or non-CNS embolism Clinically relevant bleeding 2011</td>
</tr>
</tbody>
</table>

AF=atrial fibrillation. INR=international normalised ratio. *Since this paper went to press, the BOREALIS trial comparing idarabiotaparinux with warfarin has been stopped prematurely after Sanofi-Aventis announced that it will stop the development of idarabiotaparinux. http://www.medicineandtechnology.com/2009/12/sanofi-aventis-ends-development-of.html (accessed January 29, 2010).
dabigatran will need to be administered twice daily and has a greater risk of non-haemorrhagic side-effects (ie, dyspepsia), which may increase the likelihood of drug discontinuation.

**Factor Xa inhibitors**

Several oral and subcutaneous factor Xa inhibitors are currently undergoing clinical evaluation (table 4). These include rivaroxaban,7,8,26 apixaban,7,9 and edoxaban,27 which are currently being compared with warfarin. Apixaban is also being compared with aspirin.8 Once weekly, subcutaneous idrabiotaparinux, which is identical to idraparinux except for a biotin moiety that allows neutralisation by 100 mg avidin,79 is currently being compared with warfarin.80

**Novel vitamin K antagonists**

Tecarfarin (ATI-5923) is an orally administered vitamin K epoxide reductase antagonist that has mechanisms of action identical to those of warfarin, but is metabolised by carboxylesterases and not via the CYP pathway. This difference could potentially decrease many of the drug, food, and genetic interactions resulting from the CYP system, and improve the ability to achieve and maintain the INR in the therapeutic range. A preliminary, open-label study showed that, compared with past warfarin studies, patients taking tecarfarin had a 10% improvement in time in the therapeutic INR range over the 6–12 weeks of the study.28

**Future directions**

Although the thromboprophylactic treatments of choice are antiplatelet therapy to prevent recurrent ischaemic stroke of arterial origin and anticoagulation to prevent ischaemic stroke of cardiac origin, several questions remain. First, for patients presenting with acute TIA or ischaemic stroke of arterial origin, who are at very high early risk of a recurrent ischaemic stroke, we need to determine whether there is a more effective, and acceptably safe, antithrombotic regimen than aspirin (ie, combination of aspirin and clopidogrel, combination of aspirin and ER dipyridamole, prasugrel, ticagrelor, dabigatran, rivaroxaban, or apixaban). The planned POINT trial aims to compare clopidogrel (plus aspirin) with placebo (plus aspirin) in acute TIA.29

Second, for the long-term prevention of recurrent stroke of arterial origin, we need to identify which patients should be prescribed aspirin, clopidogrel, or the combination of aspirin and ER dipyridamole. If absolute risk is to be a guide, then robust, widely applicable, and externally validated prognostic models, based on long-term follow-up are needed. Alternative antithrombotic regimens (ie, SCH 530348) continue their evaluation in large phase 3 trials.30 Although oral anticoagulation with warfarin does not have a net benefit over aspirin, mainly because of excessive bleeding, the new oral anticoagulants may be worthy of study in patients with TIA and ischaemic stroke of arterial origin if bleeding complications can be limited.

Third, for patients who present with acute TIA or ischaemic stroke of cardiac origin, the optimum time at which to start anticoagulation, between day 2 and day 14, remains uncertain, and is currently based on empirical estimates, with and without anticoagulation, of the absolute risk of re-embolisation from the heart versus estimates of the absolute risk of haemorrhagic transformation of the fresh brain infarct. A large randomised trial is needed to address this uncertainty.

Finally, for long-term prevention of recurrent stroke of cardiac origin, dabigatran is likely to replace warfarin, aspirin, and the combination of aspirin and clopidogrel for many patients, if and once approved. However, the forthcoming results of current large trials comparing promising new anticoagulants with warfarin, such as the oral factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban, the parenteral factor Xa inhibitor, idrabiotaparinux, and the novel VKA, tecarfarin, may alter this perspective.

**Contributors**

GJH wrote the first draft of the paper and reviewed and modified all subsequent drafts. JWE reviewed the first draft of the paper and reviewed and modified all subsequent drafts.

**Conflicts of interest**

GJH has received honoraria for serving on the executive committee of the AMADEUS trial (Sanofi-Aventis), ROCKET-AF trial (Johnson & Johnson), and the BOREALIS trial (Sanofi-Aventis), for serving on the steering committee of the TRA 2°P–TIMI 50 trial, for serving on the stroke outcome adjudication committee of the RE-LY and AVERROES trials, and from Sanofi-Aventis, Boehringer Ingelheim, and Pfizer Australia for speaking at sponsored scientific symposia and consulting on advisory boards. JWE was a member of the operations committee of the RE-LY trial and has received honoraria and/or research grants from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Daiichi-Sankyo, Eli-Lilly, GlaxoSmithKline, Johnson & Johnson, Portola, and Sanofi-Aventis.

**References**


