Current and emerging therapies for stroke prophylaxis in atrial fibrillation


Atrial fibrillation (AF) increases risk of stroke fivefold. This is mainly due to cardioembolism of left atrial appendage thrombus to the cerebral circulation. Currently, the principal means of stroke prophylaxis is anticoagulation using warfarin, an oral vitamin K antagonist. However, owing to the risk of hemorrhage associated with warfarin, there is considerable interest in alternative means of stroke prophylaxis. This article summarizes the evidence that warfarin and recently developed novel oral anticoagulants (e.g., dabigatran, rivaroxaban, apixaban and tecarfarin) are effective for reducing stroke risk in AF patients. We also review the impact of newer approaches such as surgical and percutaneous left atrial appendage closure and AF-rhythm control strategies in reducing stroke risk.

Keywords: anticoagulation • apixaban • atrial fibrillation • dabigatran • left atrial appendage • novel oral anticoagulants • rivaroxaban • stroke • warfarin • watchman

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia, affecting 3–5% of the population aged greater than 65 years [1–5]. After adjustment for age, gender, hypertension and other stroke risk factors, nonvalvular AF is associated with a fivefold increase in stroke risk [6]. Overall, it accounts for 15–20% of all ischemic strokes, owing to a strong association with intracardiac thrombus and subsequent embolism [4,5,7,8]. Unfortunately, AF-related cardioembolic stroke tends to be more severe, and is associated with a 50% increased mortality and greater disability at 3 months independent of other baseline risk factors. Given the aging demographics of developed countries, the importance of AF and AF-associated stroke will increase substantially in the coming decades.

The purpose of this article is to describe current and future approaches for reducing the risk of AF-associated stroke.

Mechanism of AF-related thromboembolic stroke

Left atrial appendage (LAA) thrombus is frequently found in AF [9–12]. In 23 studies where the LAA was examined intra-operatively, by transesophageal echocardiographic (TEE) or at autopsy, intracardiac thrombus was found in approximately 13% [11,13]. In valvular AF, 57% of atrial thrombi occurred in the LAA, whereas in nonvalvular AF, 90% were located in the LAA. Overall, approximately 10% of patients with non-valvular AF will have TEE evidence of LAA thrombus; however, this risk increases substantially to 20–40% in patients with a recent history of thromboembolism [10]. It is therefore believed that AF-related stroke occurs most frequently because of embolism of LAA thrombus into the systemic circulation [14–17]. Although imprecise, case-control and population-based studies estimate the proportion of strokes attributable to cardioembolism to be as high as four out of five in AF patients [17].

Based upon this understanding, three distinct approaches have been taken to prevent AF-associated stroke:
Review: Clinical Trial Outcomes

Lim, Yap & Chin

Systemic anticoagulation

Excision or exclusion of the LAA from the systemic circulation

Restoration and maintenance of sinus rhythm

Oral anticoagulation & antiplatelet therapies

Oral anticoagulation therapy

The efficacy of systemic anticoagulation with oral vitamin K antagonists (VKAs) in reducing stroke risk in AF is well described [18]. Five primary prevention trials of oral VKAs against placebo (AFASAK [19], BAATAF [20], SPAFI [21], CAFA [22] and SPINAF [23]) and a systematic review suggest that the overall relative risk reduction (RRR) is approximately 68% (95% CI: 50–79%) [24] (Figure 1). The corresponding absolute risk reduction in these trial populations was 31 ischemic strokes prevented per year per 1000 patients treated (number needed to treat = 32). The EAFT study of secondary prevention was also consistent with these data [25].

It should be noted that these analyses were carried out using an intention-to-treat principle. Repeating the analysis after excluding participants who were not receiving assigned anticoagulation demonstrated the overall reduction in ischemic stroke was substantially greater, approaching 85% [17]. This shows that adjusted-dose warfarin, if taken carefully, virtually eliminates the increased risk of ischemic stroke associated with AF, presumably principally via inhibiting formation of atrial appendage thrombi. This has been confirmed by transesophageal echocardiographic correlations [26,27]. Oral VKAs for AF has now been in use for over 50 years.

Oral antiplatelet therapy

In contrast, the efficacy of antiplatelet agents such as aspirin is less clear (Figure 2). A meta-analysis using pooled individual patient-level data from the AFASAK, SPAFI and EAFT trials estimated a RRR of 21% compared with placebo, but with an associated 95% CI of 0–38% [28,29]. The principal trial driving these favorable results was SPAFI-I; if removed, any benefit of

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Target INR</th>
<th>Warfarin RR (%)</th>
<th>Control RR (%)</th>
<th>RRR (%) and 95% CI</th>
</tr>
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<tbody>
<tr>
<td>AFASAKI</td>
<td>671</td>
<td>2.8–4.2</td>
<td>2.7</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>SPAFI</td>
<td>421</td>
<td>2.0–4.5</td>
<td>3.8</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>BAATAF</td>
<td>420</td>
<td>1.5–2.7</td>
<td>1.4</td>
<td>6.3†</td>
<td></td>
</tr>
<tr>
<td>CAFA</td>
<td>378</td>
<td>2.0–3.0</td>
<td>3.2</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>SPINAF</td>
<td>571</td>
<td>1.4–2.8</td>
<td>2.5</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>EAFT</td>
<td>439</td>
<td>2.5–4.0</td>
<td>8.9†</td>
<td>23.4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2000</td>
<td></td>
<td>2.7</td>
<td>9.2</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Stroke: adjusted-dose warfarin versus placebo/control.

†Several oral vitamin K antagonists used.

‡46% of exposure aspirin in control group.

INR: International normalized ratio; RR: Risk reduction; RRR: Relative risk reduction.

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antplatelets would be greatly attenuated or lost altogether. Even in SPAF-I, the effect of aspirin was attenuated in patients older than 75 years old, and aspirin did not prevent severe or recurrent strokes.

It is notable that this RRR is similar to the RRR reported for stroke reduction in high-risk patients with vascular disease treated with antplatelets by the Antithrombotic Trialists’ Collaboration [30]. Since AF patients frequently have vascular disease, the observed effect of antplatelet agents in AF might simply be derived from prevention of ischemic stroke rather than cardioembolic stroke. At a pathophysiological level, this makes sense since thrombi in AF are fibrin-rich red clots that would not be expected to respond to antplatelet agents (in contrast to the platelet-rich white clots seen in vascular disease).

### Oral anticoagulants compared with oral antplatelets

Consistent with this, meta-analysis of oral VKAs versus antplatelet agents consistently favors the former over the latter (RRR: 39%; 95% CI: 22%–52%) [28]. The

![Figure 2. Stroke: antplatelet agents versus placebo/control.](image)

**Figure 2.** Stroke: antplatelet agents versus placebo/control.

RR: Risk reduction; RRR: Relative risk reduction.

Reproduced with permission from [28].
largest of these to date was the ACTIVE-W trial [31], and pitted oral VKAs against dual antiplatelet therapy with aspirin and clopidogrel. Even with dual antiplatelet agents, oral VKAs was more effective (RRR: 40%; 95% CI: 18%–56%).

- **Combinations of oral VKAs & antiplatelet therapy**

Other strategies including low-dose oral VKAs (VKAs titrated to an international normalized ratio [INR] range <2.0–3.0), fixed low-dose oral VKAs, oral VKAs with single or dual antiplatelet therapy have been tried. So far, there is no consistent evidence that any of these strategies perform better than oral VKAs titrated to an INR of 2.0–3.0 ([Figure 3](#))[18].

- **Summary**

The evidence supporting the efficacy of oral VKAs titrated to an INR of 2.0–3.0 for stroke prophylaxis in AF patients is strong. Nevertheless, despite the convincing study data supporting the efficacy of oral VKAs, real-world use is fraught with difficulty [32]. There is significant inter- and intra-patient variability in dose–response, the therapeutic index is narrow, numerous drug and

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**Study** | **Patients (n)** | **Target INR** | **Warfarin RR (%)** | **Antiplatelet RR (%)** | **RRR (%)** | **95% CI**
--- | --- | --- | --- | --- | --- | ---
AFASAK I | 671 | 2.8–4.2 | 2.7 | 4.8 |  |  |
AFASAK II | 339 | 2.0–3.0 | 6.5 | 5.3 |  |  |
Chinese ATAFS | 704 | 2.0–3.0 | 2.7 | 4.6 |  |  |
EAF | 455 | 2.5–4.0 | 8.9 | 22.6 |  |  |
PATAF | 272 | 3.5 | 2.3 | 2.8 |  |  |
SPAF II | 1100 | 2.0–4.5 |  |  |  |  |
Age ≤75 years | 715 | 5.3 | 5.9 |  |  |  |
Age >75 years | 385 | 10.2 | 11.2 |  |  |  |
**Total aspirin trials** | **3647** | **5.0** | **7.7** |  |  |  |
SIFA (indobufen) | 916 | 2.0–3.5 | 4.0 | 5.0 |  |  |
ACTIVE-W (clop. + asp.) | 6706 | 2.0–3.0 | 1.9 | 3.2 |  |  |
NASPEAF (triflusial) | 479 | 2.0–3.0 | 2.3 | 4.5 |  |  |
**Total antiplatelet trials** | **11748** | **3.1** | **4.8** |  |  |  |
**Secondary prevention trials – 22%**

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**Figure 3.** Stroke: adjusted-dose warfarin versus antiplatelet therapy.

*Includes two small trials (n = 106) with only two strokes. Does not include SPAF III (n = 341) where antiplatelet groups also received warfarin.

INR: International normalized ratio; RR: Risk reduction; RRR: Relative risk reduction.

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dietary interactions exist, laborious laboratory monitoring is needed [33] and bleeding complications may be severe or life threatening (particularly intracranial hemorrhage). Correspondingly, oral VKAs are contraindicated in 14–44% of otherwise eligible patients [34]. Even in eligible patients, oral VKAs are prescribed in only 15–66% of patients [34]. Finally, in patients receiving oral VKAs, the time-in-therapeutic range (TTR) (i.e., proportion of time where the INR was in target range) is often low [33], suggesting that the benefits of oral VKAs may not be completely realized in clinical practice.

■ Novel anticoagulant agents

Given these limitations, there have been extensive efforts from the pharmaceutical industry to develop new anticoagulant agents [35] (Table 1 & 2, Figure 4). Broadly, the new oral anticoagulants now fall into three categories: the oral direct thrombin inhibitors (ximelagatran and dabigatran), the oral factor Xa inhibitors (rivaroxaban and apixaban) and an oral VKA variant (tecarfarin). The landmark clinical trials involving the use of these agents for stroke prophylaxis in AF are summarized in Table 2.

■ Oral direct thrombin inhibitors

Ximelagatran

The earliest of these to pass Phase III clinical trials was ximelagatran [36], a prodrug that is converted in vivo by the liver and other peripheral tissues via dealkylation and dehydroxylation to the active agent, melagatran. Its chief advantages over oral VKAs are predictable and rapid onset of action without the need for laboratory monitoring. Potential disadvantages are the absence of an antidote, and relatively short half-life. Subsequently, it became clear that ximelagatran could result in liver toxicity even following drug withdrawal, leading to cessation of further development in 2006.

Dabigatran & RE-LY

Dabigatran is a derivative of the benzamidine-based thrombin inhibitor N-(2-naphthylsulfonylglycyl)-4-amidinophenylalanine piperidide, which has been known since the 1980s as a powerful inhibitor of various serine proteases, including thrombin. Addition of a hydrophobic side chain to form dabigatran etexilate enables oral bioavailability. It is mainly excreted via the renal route. So far, this drug appears to have a good safety profile. Its chief side effect is dyspepsia, which is unfortunate since proton pump inhibitors reduce absorption.

The RE-LY trial is the key study that led to US FDA approval in October 2010 of dabigatran for stroke prophylaxis in nonvalvular AF [37]. RE-LY used a prospective randomized open trial with blinded endpoint evaluation. It evaluated the efficacy and safety of two different doses of dabigatran relative to warfarin in patients with AF plus one additional risk factor. A total of 18,113 patients were enrolled, 50% of whom were warfarin naive. Participants were randomly allocated to one of three arms:

* Adjusted-dose warfarin
* Dabigatran 110 mg b.i.d.
* Dabigatran 150 mg b.i.d.

The mean TTR was 64% (INR range 2.0–3.0).

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**Table 1. Comparative properties of four novel oral anticoagulants.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Administration per day</th>
<th>Bioavailability (%)</th>
<th>Half-life (h)</th>
<th>Monitoring</th>
<th>Metabolism and elimination</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Vitamin K epoxide reductase</td>
<td>Once</td>
<td>&gt;95</td>
<td>40</td>
<td>INR-adjusted</td>
<td>Hepatic (CYP 2C9, 3A4, 1A2); urine (92%), feces (8%)</td>
<td>CYP 2C9, 1A2, 3A4</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
<td>Thrombin</td>
<td>Once/twice</td>
<td>6</td>
<td>14–17</td>
<td>Not needed</td>
<td>Renal (80%), fecal (20%)</td>
<td>P-gp inhibitors</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Factor Xa</td>
<td>Once/twice</td>
<td>&gt;80</td>
<td>5–13</td>
<td>Not needed</td>
<td>CYP 3A4; renal (66%) fecal (33%)</td>
<td>Potent CYP 3A4 inhibitors and P-gp inhibitors</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Factor Xa</td>
<td>Twice</td>
<td>&gt;50</td>
<td>8–15</td>
<td>Not needed</td>
<td>CYP 3A4; renal (27%) fecal (25%)</td>
<td>Potent CYP 3A4 inhibitors and P-gp inhibitors</td>
</tr>
<tr>
<td>Tecarfarin</td>
<td>Vitamin K epoxide reductase</td>
<td>Once</td>
<td>80–90</td>
<td>119</td>
<td>INR-adjusted</td>
<td>Hepatic carboxylesterase; feces (~57%), urine (33%)</td>
<td>Limited (not metabolized by CYP450)</td>
</tr>
</tbody>
</table>

INR: International normalized ratio; P-gp: P-glycoprotein.
For the primary efficacy end point, which was a composite of stroke and systemic embolism, warfarin and dabigatran 110 mg were equivalent (1.71 and 1.54%, respectively; p = 0.34), while dabigatran 150 mg was significantly more effective than either warfarin or dabigatran 110 mg (1.11%/year; p < 0.001). For the primary safety end point, major bleeding occurred significantly less often with dabigatran 110 mg than warfarin (2.87 vs 3.57%; p = 0.003) while dabigatran 150 mg demonstrated similar bleeding rates to warfarin (3.36%; p = 0.31). In the original report of the RE-LY data, there was a significant increase in the rate of myocardial infarction in patients treated with dabigatran 150 mg compared with warfarin; however, a subsequent analysis that included silent myocardial infarctions based on the development of new pathologic Q waves on the electrocardiogram did not show a significant difference.

RE-LY, therefore, showed that there were two effective doses of dabigatran, but with differing risk–benefit profiles. Importantly, this trial also proved that it was possible to reduce stroke risk compared with oral VKAs, without simultaneously increasing bleeding risk – this was not clear at the outset.

### Oral factor Xa inhibitors

Factor Xa is a promising therapeutic target for anticoagulation because of its key position in the coagulation cascade, at the juncture between the extrinsic (tissue...
factor initiated) and intrinsic (surface activation and amplification) pathways. Together with phospholipids, calcium ions and factor Va, it comprises the prothrombinase complex, which is responsible for the generation of thrombin from prothrombin. Although factor Xa inhibition attenuates the generation of thrombin, it does not affect thrombin activity, thereby preserving hemostasis, which in clinical terms, may translate to efficacy with lower bleeding. Fondaparinux is an indirect factor Xa inhibitor already in clinical use, providing clinical proof of principle; unfortunately, it must be administered parenterally.

However, two new anti-factor Xa agents with good oral bioavailability have now been developed – rivaroxaban and apixaban. These inhibitors directly engage the active center of the factor Xa molecule, thereby inhibiting both free factor Xa in plasma and factor Xa attached to the prothrombinase complex. In vitro, Factor Xa activates clotting over a wider concentration range than thrombin. Consequently, the newly developed direct factor Xa inhibitors may have a wider therapeutic index than thrombin inhibitors.

Rivaroxaban
Rivaroxaban is an oxazolidinone derivative that selectively inhibits both free factor Xa and prothrombinase-bound factor Xa. It has several desirable clinical characteristics: good oral bioavailability, very predictable pharmacokinetics across a wide spectrum of patients, as well as a flat dose–response curve across an eightfold dose range (5–40 mg). Its half-life is substantially lower than dabigatran but once-daily dosing

Figure 4. The coagulation cascade and target proteins of key novel oral anticoagulants. Reproduced with permission from [35].

New oral Xa inhibitors
Rivaroxaban
Apixaban
Betrixaban
Edorabran
Darexaban (YM150)

New oral IIa inhibitors
Ximelagatran
Dabigatran
still appears effective. Dose adjustment is needed with renal impairment, and it is contraindicated when creatinine clearance is less than 15 ml/min. It is also contraindicated with liver disease owing to lack of data.

The landmark study of rivaroxaban was ROCKET-AF [38], a study with many similarities to RE-LY. ROCKET-AF was a randomized double-blind, double-dummy trial comparing rivaroxaban with warfarin. Inclusion criteria were AF within the 6-month period preceding randomization, plus two or more risk factors. A total of 14,264 patients were enrolled. The mean CHADS2 score was substantially higher than in RE-LY (3.5 vs 2.1), as expected. For the warfarin cohort, mean TTR was 57.8%.

For the primary efficacy end point of stroke and non-CNS embolism, non-inferiority of rivaroxaban was established using an on-treatment analysis (2.12 vs 2.42%, respectively; p = 0.117). When assessed for superiority using intention-to-treat, rivaroxaban did not reach non-inferiority criteria compared with warfarin (hazard ratio [HR]: 0.88; 95% CI: 0.74–1.03). When superiority was tested using a less stringent on-treatment analysis, rivaroxaban just met the criteria (HR: 0.79; 95% CI: 0.65–0.95).

In terms of the primary safety end point, major bleeding rates were similar with rivaroxaban and warfarin (3.6 vs 3.45%, respectively; p = 0.570); however, rates of intracranial hemorrhage were significantly lower with rivaroxaban (0.49 vs 0.74%; p = 0.019).

Apixaban
Apixaban is another oral direct factor Xa inhibitor with similarities to rivaroxaban. The key trial of apixaban in AF, ARISTOTLE [39], which compares it against warfarin, is currently ongoing. However, the AVERROES study [40,41], comparing apixaban to aspirin, has been reported. This was a randomized open-label comparison of apixaban 5 mg b.i.d versus aspirin 81–324 mg once daily in patients with AF plus one risk factor and not suitable for oral VKAs. A total of 5600 patients were recruited. Mean CHADS2 score was 2.1. The primary efficacy end point was stroke and systemic embolism, occurring in 3.9 and 1.7% of the aspirin- and apixaban-treated patients, respectively (p < 0.001). As a result of this highly significant RRR of over 55%, the trial was halted early. The rates of major bleeding were not significantly different between the two agents (1.2 vs 1.4%, respectively). In addition, apixaban was better tolerated than aspirin; the rate of permanent discontinuation was 17.9% per year for apixaban versus 20.5% for aspirin (HR: 0.88; 95% CI: 0.78–0.99; p = 0.03).

On this basis, the data indicates that in patients who cannot take oral VKAs, apixaban is a superior alternative to aspirin. However, until the ARISTOTLE trial [39] reports, it is uncertain whether apixaban is superior to oral VKAs.

Other direct Xa inhibitors
Less developed oral direct Xa inhibitors include betrixaban (Portola Pharmaceuticals, San Francisco, CA, USA), edoxaban (Daiichi Sankyo, Inc, Parsippany, NJ, USA) and darexaban (YM150; Astellas Pharma, Tokyo, Japan). Phase II trials have been completed for each and Phase III studies are pending.

Tecarfarin
Tecarfarin (ATI-5923) is a novel oral VKA with a mechanism of action identical to warfarin. It is a structural analogue of warfarin, which is metabolized by carboxylesterases in the hepatic microsomes, yielding a single inactive metabolite. This contrasts with warfarin, which is metabolized by the cytochrome P450 system. Therefore, unlike warfarin, tecarfarin is not subject to cytochrome P450–mediated drug–drug or drug–food interactions or genetic cytochrome P450 variants but can still be monitored with the INR. In a small Phase IIa study of 66 AF patients given tecarfarin, the mean interpolated TTR was substantially better than in RE-LY (3.5 vs 2.1), as expected. For the warfarin cohort, mean TTR was 57.8%.

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In patients with no stroke risk factors (e.g., lone AF), the potential for adverse effects, especially bleeding.

### North America

On 19 October 2010, the FDA similarly approved dabigatran for the "prevention of stroke and systemic thromboembolism in patients with nonvalvular AF". On February 2011, the American College of Cardiology Foundation, American Heart Association and Heart Rhythm Society released a focused update to their combined AF management guidelines to reflect this, including dabigatran as an “alternative to warfarin for prevention of stroke or systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization, without a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure or advanced liver disease” (class I recommendation, Level of Evidence B) [45]. However, the guidelines also note, “because of the b.i.d dosing and greater risk of nonhemorrhagic side effects with dabigatran, patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran”. This is supported by subanalysis of the RE-LY data showing the benefits of dabigatran vis-à-vis all vascular events, nonhemorrhagic events and mortality was significantly attenuated compared with warfarin in centers able to maintain a high TTR [46]. However, dabigatran was better than warfarin at reducing intracranial hemorrhage, irrespective of quality of INR control.

Interestingly, the FDA approved dabigatran 150 mg b.i.d. but not dabigatran 110 mg b.i.d. Furthermore, the FDA approved dabigatran 75 mg b.i.d. for patients with severe renal impairment (a dose which was never tested in the RE-LY trial). The controversy surrounding this decision led to a perspective article in the *New England Journal of Medicine* authored by the FDA [47], wherein they explain their reasoning. Essentially, the FDA were “unable to find any population for whom the availability of a lower (110 mg b.i.d.) dose would improve dabigatran’s benefit–risk profile, and it appeared clear that most, if not all, patients should receive the higher (150 mg b.i.d.) dose”. The decision to approve an untested 75 mg b.i.d. dose for patients with severe renal failure was “based not on efficacy and safety data, but on pharmacokinetic and pharmacodynamics modeling”, in common with most dose adjustments relating to renal impairment.

Novel oral anticoagulants other than dabigatran

As further clinical trial data emerges, these will likely receive regulatory approval and incorporation into guidelines.
LAA exclusion

The LAA is an elongated cul-de-sac attached to, but anatomically and embryologically distinct from, the left atrial body [48,49]. It is the embryonic left atrial remnant that developed during the third week of gestation. It has a complex morphology that is highly variable between individuals. In one autopsy study, 54% had two lobes and 34% had three or more lobes [2]. In AF, blood flow is often slow within the LAA, and, as noted previously, hemostasis appears to be the primary mechanism promoting thrombus formation.

Excision, ligation, suturing and stapling techniques have been developed to exclude the LAA from the systemic circulation [14,50,51]. These can be performed during open-heart surgery, using minimally invasive techniques or more recently, via percutaneous methods. Important differences may exist between these approaches.

Surgical approaches to the LAA

Hellerstein and colleagues first reported the feasibility of canine LAA resection in 1947 [52,53]. Soon after, several investigators demonstrated that, although technically challenging, this could also be accomplished in humans, and in several small case series, appeared to reduce stroke risk. In 2000, Johnson et al. reported a large case series with 437 patients who underwent adjunctive prophylactic LAA excision using suture or stapling, including 17 with pre-existing AF. No acute bleeding or other significant late problems were identified, and no later stroke could be attributed to AF [50].

Subsequently, however, five studies showed a high rate of incomplete LAA occlusion using suture or staple techniques, as documented by follow-up TEE, ranging from 10–83%, together with several stroke events [13]. As these were not randomized controlled studies, the efficacy of LAA exclusion could not be evaluated. Indeed, a small cohort study suggested that there might be an increased risk of stroke among patients undergoing LAA occlusion, possibly owing to the high rates of incomplete LAA occlusion [54]. Other potential complications include bleeding and heart failure [55,56]. As 30% of atrial natriuretic peptide is produced in the atrial appendages [57], removal of one or both may significantly impair volume regulation. Where biatrial appendectomies have been performed as part of MAZE operations, this appears to be a real concern.

These considerations led to the design of the ongoing LAA study, LAOOS [58], which is a randomized controlled trial to evaluate the efficacy of LAA occlusion in patients undergoing elective coronary artery bypass grafting with any of four prespecified risk factors for AF: age >75 years, hypertension, age >65 years and/or previous stroke or history of AF. Pilot results showed surgical LAA exclusion using the authors’ methods did not significantly prolong the duration of surgery, could be accomplished in >90% and was safe, with no increase in perioperative bleeding or diuretic use. However, the complete study and follow-up have not yet reported.

In summary, surgical LAA exclusion is currently widely accepted, but the evidence base is limited. Nevertheless, in many centers, it is routine practice to remove the LAA during mitral-valve surgery, given the often very high risk of AF and thromboembolism. The final results of LAOOS should help address on-going concerns about the efficacy and safety of surgical LAA exclusion in this and other clinical contexts.

Percutaneous approaches to the LAA

Percutaneous occlusion of the LAA can be accomplished using three devices:

- Percutaneous LAA Transcatheter Occlusion device (PLAATO®; ev3, Plymouth, Minnesota, USA)
- AMPLATZER® device (AGA Medical Corp, North Plymouth, Minnesota, USA)
- WATCHMAN LAA® device (Atritect Inc, Minneapolis, Minnesota, USA)

The basic principles of LAA exclusion are similar in each. Venous access is obtained via the femoral vein, and the LAA is approached from the right atrium via a transseptal puncture, patent foramen ovale (PFO) or atrial septal defect (ASD) if present. LAA localization is achieved by either TEE or fluoroscopic contrast injection, or both. The aim is to deploy a device to occlude the LAA ostium, induce controlled thrombosis within the LAA cavity and simultaneous growth of the endocardium over the atrial surface of the device. Accordingly, all three devices consist of a nitinol frame with some form of anchoring mechanism, covered by a polymeric membrane designed to encourage endothelialisation.

PLAATO

Two landmark studies showing the safety and feasibility of the PLAATO device have been published [59]; these were nonrandomized multicenter registries. LAA occlusion was successful in 108 of 111 (97.3%) patients with nonrheumatic AF at high risk of ischemic stroke and not suitable for oral anticoagulation therapy. Nine procedure-related serious adverse events occurred in seven patients, but none of the serious adverse events were device-related. Successful LAA occlusion was documented in 98% at the 6-month follow-up TEE. No mobile thrombus, mitral-valve damage, pulmonary-vein

LAA exclusion

The LAA is an elongated cul-de-sac attached to, but anatomically and embryologically distinct from, the left atrial body [48,49]. It is the embryonic left atrial remnant that developed during the third week of gestation. It has a complex morphology that is highly variable between individuals. In one autopsy study, 54% had two lobes and 34% had three or more lobes [2]. In AF, blood flow is often slow within the LAA, and, as noted previously, hemostasis appears to be the primary mechanism promoting thrombus formation.

Excision, ligation, suturing and stapling techniques have been developed to exclude the LAA from the systemic circulation [14,50,51]. These can be performed during open-heart surgery, using minimally invasive techniques or more recently, via percutaneous methods. Important differences may exist between these approaches.

Surgical approaches to the LAA

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obstruction, device migration or dislodgement was observed. During the average follow-up of 9.8 months, the observed versus estimated annual stroke risk was 2.2 and 6.3%, respectively, representing a 65% RRR. Longer term follow-up has recently been published[60]; two patients had thrombus either at the surface of the occluding device or on the interatrial septum; however, MRI showed no new strokes.

Unfortunately, despite implantation of several hundred devices and these promising initial results, PLAATO was withdrawn from the market in 2006 owing to the overly large financial investment projected to obtain regulatory approval.

AMPLATZER
AMPLATZER devices were originally developed for the transcatheter closure of structure heart defects, principally PFOs and ASDs. In 2002, initial attempts using AMPLATZER ASD, VSD or PFO closure devices for LAA occlusion proved successful in 16 patients[61]. At an average follow-up of 5 years, all the LAAs were completely occluded with no evidence of thrombosis on the atrial aspect of the device. On the basis of these promising results, the AMPLATZER Cardiac Plug was specifically developed.

The AMPLATZER Cardiac Plug received CE-Mark certification in December 2008. The ongoing Cardiac Plug European Registry is also expected to report soon.

WATCHMAN
The first generation of WATCHMAN devices had a relatively high complication rate, including device embolizations, delivery-wire fracture and air embolism; however, current generation devices have a modified design and appear much more robust. An important difference compared with the other devices is that a period of anticoagulation after device implantation is needed (at least 45 days); thereafter, long-term antiplatelet therapy is recommended.

The landmark PROTECT-AF study has now reported[62]. This was a prospective randomized controlled non-inferiority trial comparing LAA closure using the WATCHMAN device against long-term warfarin therapy; 707 patients from 59 centers in the USA and Europe were randomized 2:1, respectively. Inclusion criteria included patients with nonvalvular AF with at least one of the following: previous stroke or transient ischemic attack, congestive heart failure, diabetes, hypertension or age 75 years or older. Patients were followed up by TEE at 45 days, 6 months and 1 year, together with biannual clinic follow-up for up to 5 years. At a 1065 patient-years of follow-up the primary efficacy event rate was 3.0 per 100 patient-years (95% credible interval: 1.9–4.5) in the device group and 4.9 per 100 patient-years (2.8–7.1) in the control group (rate ratio: 0.62; 95% CI: 0.35–1.25). The probability of non-inferiority of the intervention was >99.9%.

In terms of safety, the primary end point was a composite of stroke, cardiovascular death and systemic embolization. These were more frequent in the device group (7.4 per 100 patient-years [95% CI: 5.5–9.7] versus 4.4 per 100 patient-years [95% CI: 2.5–6.7]; RR: 1.69; 1.01–3.19), mainly as a result of periprocedural complications. These included pericardial effusion requiring drainage (5%), acute ischemic stroke due to air or thromboembolism (1%), device embolization and removal (<1%) and postimplantation sepsis and removal (<0.5%). Subsequent work suggests that complication rates are operator dependent and may fall with greater experience[63].

On the basis of this study, the WATCHMAN device received conditional FDA approval on 23 April 2009. Approval was subject to implantation only in centers with surgical backup, as well as institution of a physician certification program. The FDA also recommended the creation of a registry and extended follow-up of current clinical trials.

In summary, percutaneous closure of the LAA is feasible, and appears to be effective in reducing stroke risk in experienced hands. The best evidence to date is for the WATCHMAN device. Further confirmatory studies as well as expansion of the population suitable for device implantation can be expected in the future.

Restoration & maintenance of sinus rhythm

Lessons from pharmacotherapy for AF
In 2000, the PIAF study demonstrated that a strategy of rate control in AF was not inferior to one of rhythm control with respect to quality of life measures[64] (Table 3). Although small, comprising of only 252 patients followed up over a period of 1 year, it is historically important, because it marks the start of a series of randomized controlled trials comparing rate versus rhythm control in AF. In the absence of data prior to this study, it had been assumed that restoration and maintenance of sinus rhythm in AF patients would be associated with lowered stroke rates. The two landmark studies to formally test this hypothesis using anti-arrhythmic drugs (AADs) are AFFIRM and RACE (Table 3)[65,66].

AFFIRM
This was a large prospective, randomized controlled trial including 4060 patients[65]. The principle enrollment criteria were: patients aged 65 years or more, or who had other risk factors for stroke or death; a high likelihood of recurrent AF; AF likely to cause illness or death; need for long-term treatment for AF; no contraindications for long-term anticoagulant therapy; eligibility for either rate or rhythm strategies.
Table 3. Rhythm- versus rate-control strategies in atrial fibrillation.

<table>
<thead>
<tr>
<th>Trial (year)</th>
<th>Patients (n)</th>
<th>Inclusion Therapy</th>
<th>% SR in rhythm control cohort</th>
<th>Primary outcome Result</th>
<th>Rhythm</th>
<th>Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIAF (2000)</td>
<td>252</td>
<td>Symptomatic persistent AF</td>
<td>Diltiazem vs amiodarone/DCCV</td>
<td>56% at 1 year Symptomatic improvement</td>
<td>55.1%</td>
<td>60.8%</td>
<td>0.317</td>
</tr>
<tr>
<td>AFFIRM (2002)</td>
<td>4060</td>
<td>Recurrent AF, &gt;65 years or risk factors for stroke or death</td>
<td>Physician discretion</td>
<td>62.6% at 5 years Overall mortality</td>
<td>23.8%</td>
<td>21.3%</td>
<td>0.08</td>
</tr>
<tr>
<td>RACE (2002)</td>
<td>522</td>
<td>Recurrent persistent AF for &lt;1 year, prior DCCV</td>
<td>Digitalis, nonhydropyridine CCB + β blocker vs DCCV/sotalol/ flecainide/proprafenone/amiodarone</td>
<td>39% at end of follow-up Composite (CVD death, heart failure, thromboembolism, bleeding, pacemaker implantation and severe adverse side effects of drugs)</td>
<td>22.6%</td>
<td>17.2%</td>
<td>0.11</td>
</tr>
<tr>
<td>STAF (2003)</td>
<td>200</td>
<td>AF (for 4 weeks–2 years), LA: 45-70mm, CCF, NYHA: II–IV, LVEF: 20–45%, prior DCCV</td>
<td>Physician discretion</td>
<td>23% at 3 years Composite (death, CVA/TIA, systemic embolism and cardiopulmonary resuscitation)</td>
<td>5.54%/year</td>
<td>6.09%/year</td>
<td>0.99</td>
</tr>
<tr>
<td>AF-CHF (2008)</td>
<td>1376</td>
<td>AF (for ≥6 h or needing DCCV), LVEF ≤35%, CCF</td>
<td>β blocker with digitalis vs DCCV/amiodarone/sotalol/dofetilide</td>
<td>73% at 4 years CVD death</td>
<td>27%</td>
<td>25%</td>
<td>0.59</td>
</tr>
<tr>
<td>EURIDIS/ADONIS (2007)</td>
<td>1237</td>
<td>AF in preceding 3 months but SR for ≥1 h prior to randomization</td>
<td>Placebo vs dronedarone</td>
<td>35.9% at 1 year (dronedarone) Time to first recurrence of AF Hospitalization or death</td>
<td>116 days (dronedarone) 22.8% (dronedarone)</td>
<td>53 days (placebo) 30.9% (placebo)</td>
<td>&lt;0.05 0.01</td>
</tr>
<tr>
<td>ATHENA (2009)</td>
<td>4628</td>
<td>Paroxysmal or persistent AF with 1 or more of: &gt;70 years, DM, CVA/TIA, systemic embolism, LA: ≥50 mm or EF: ≤40%</td>
<td>Placebo vs dronedarone</td>
<td>– First hospitalization due to cardiovascular events or death from any cause</td>
<td>31.9% (dronedarone) 39.4% (placebo)</td>
<td>–</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AF: Atrial fibrillation; CCB: Calcium-channel blocker; CCF: Congestive cardiac failure; CVA: Cerebrovascular accident; CVD: Cardiovascular disease; DCCV: DC cardioversion; DM: Diabetes mellitus; LA: Left atrium; LVEF: Left ventricular ejection fraction; SR: Sinus rhythm; TIA: Transient ischemic attack.
At 5 years, there were more deaths among those assigned to rhythm control compared with the rate control, although this did not reach statistical significance (356 vs 310; HR: 1.15; 95% CI: 0.99–1.34; \( p = 0.08 \)). Further, there were more hospitalizations and adverse drug effects associated with rhythm control. Although not powered to examine ischemic stroke as an end point, there was also a nonsignificant increase in the rhythm control cohort (7.1 vs 5.5%; \( p = 0.79 \)). This may be partly or fully accounted for by the increased likelihood of discontinuing warfarin by physicians in the rhythm control group; the rate of warfarin usage was 70 versus 85%, respectively.

**RACE**

This was a study of 522 patients with recurrent persistent AF or flutter, measuring a composite end point of cardiovascular death, heart failure, thromboembolic complications, bleeding, pacemaker implantation, and severe drug-related adverse effects [66]. After a mean follow-up of 2.3 years, the primary end point occurred in 17.2% in the rate control group compared with 22.6% in the rhythm control group. Using a prespecified criterion for non-inferiority of ≤10%, rate control was not inferior to rhythm control. As in AFFIRM, there was a slightly higher incidence of thromboembolic complications in the rhythm control group.

**AF-CHF**

PIAF, STAF [67], AFFIRM and RACE predominantly recruited patients with relatively preserved left ventricular ejection fraction; the more recent AF-CHF study [68] has now also confirmed that AADs were not effective in reducing either mortality or stroke risk in the important subgroup of AF patients with impaired left ventricular function (ejection fraction of ≤35%).

Taken at face value, all these studies show rate control strategies are not inferior to rhythm control with respect to quality of life, total mortality or stroke risk. However, there is an important caveat.

All studies to date have documented poor efficacy of the AADs in maintaining sinus rhythm; in PIAF, AFFIRM and RACE, the proportion of patients randomized to rhythm control who were actually in sinus rhythm at the end of follow up was only 56, 62.5 and 39%, respectively. There were also high rates of side-effects and crossover, and an increase in mortality that may have been directly contributed to from pro-arrhythmic effects of the drugs used.

**Dronedarone & ATHENA**

Dronedarone is an AAD that recently gained FDA approval, but was not used in either AFFIRM or RACE. It is a benzofuran derivative of amiodarone, which has significantly reduced extracardiac toxicity as well as improved pharmacokinetic properties compared with amiodarone. In the ATHENA study [69], which included 4628 AF patients and compared dronedarone to placebo, dronedarone was associated with a significantly reduced hazard of death (2.7 vs 3.9%, respectively, over a follow-up period of 21 months; HR: 0.71; 95% CI: 0.51–0.98; \( p = 0.03 \)). This was largely due to a reduction in arrhythmic death.

Interestingly, in post hoc analysis, there also appeared to be a reduction in stroke risk from 1.8% per year to 1.2% per year (HR: 0.66; 95% CI: 0.46–0.96; \( p = 0.027 \)) [70]. This effect of dronedarone was similar whether or not patients were receiving oral anticoagulant therapy, and there was a significantly greater effect of dronedarone in patients with higher CHADS2 scores. Even given these possible benefits of dronedarone, this agent still has to be used with caution; in the ANDROMEDA study that enrolled patients with impaired left ventricular systolic function, dronedarone increased mortality [71].

**Summary**

The above data demonstrate that general equivalence of current rhythm- and rate-control strategies may more properly be interpreted as showing a failure of AAD efficacy at maintaining sinus rhythm. It does not preclude the possibility that in the future more effective and safer means of maintaining sinus rhythm might in fact be able to lower stroke risk and/or total mortality. It appears this may be the case for dronedarone; proof of this property of dronedarone will require replication in future studies.

- **Nonpharmacologic techniques to restore & maintain sinus rhythm**

Improved understanding of the mechanisms underlying AF has led to the development of nonpharmacological methods of restoring and maintaining sinus rhythm. In 1987, Cox et al. pioneered the surgical MAZE procedure, demonstrating that a series of biatrial full-thickness incisions during open-heart surgery could abolish AF by blocking the macroreentry circuits needed to sustain the arrhythmia [72–74]. Subsequently, percutaneous catheter ablation techniques involving pulmonary-vein isolation, targeting of fractionated electrogids, autonomic ganglionated plexi, atrial compartmentalization or combinations of these lesion sets, have also been successfully used to restore and maintain sinus rhythm.

The reported long-term success rate of the surgical maze in maintaining sinus rhythm appears significantly better than for AADs, varying between 70 and 90% at 1 year [75]. In one recent series of 258 patients...
scheduled for elective open-heart surgery with preoperative permanent AF and structural heart disease, a concomitant radiofrequency modified maze was performed; 69% were in sinus rhythm at 1 year, 56% at 3 years, 52% at 5 years and 57% at the latest reported follow up [76]. Stroke rates were significantly lower than expected (1.6%), but 99% of patients were maintained on oral anticoagulation. For percutaneous catheter ablation, despite the plethora of techniques that have been used to successfully restore sinus rhythm, there is no evidence to favor one technique over another. Overall, arrhythmia-free survival of 56–89% at 1 year has been reported, although multiple procedures may be needed. However, longer term follow-up has recently been documented, and the data do not appear as favorable. In one report, 5-year arrhythmia-free survival was only 29% [77].

So far, the impact of either surgical or catheter AF ablation on stroke risk has not been properly examined in randomized controlled trials. However, given the high recurrence rates of AF in the long-term, in patients where long-term oral anticoagulation is indicated, discontinuation cannot currently be recommended even after apparent successful ablation.

**Prediction of stroke risk**

Consequently, a large number of risk-stratification models (RSMs) to quantify individual stroke risk in AF have been developed. In general, these RSMs are derived either from expert consensus, which are subsequently validated in clinically relevant populations, or by systematic review of the literature, to identify the most predictive variables that are then used to construct the RSM. Systematic review identifies the most highly predictive variables as history of stroke or transient ischemic attack, increasing age, hypertension and structural heart disease (left ventricular dysfunction or hypertrophy), whereas the evidence regarding diabetes mellitus, gender and other patient characteristics are less consistent.

The most widely applied RSM is the CHADS2 index, probably because of its simplicity and wide applicability. It achieves this by incorporating only clinical risk factors into the index – one point each is assigned for a history of congestive heart failure, hypertension, age ≥ 75 years and diabetes, and two points for a history of stroke or transient ischemic attack. A score of 0 represents low risk, 1 represents intermediate risk and 2 or more represents high risk. This RSM evolved from the AF Investigators and Stroke Prevention in AF (SPAF) criteria, and was developed by consensus expert opinion; however, it has since been clinically validated in a number of populations.

Unfortunately, all RSMs to stratify stroke risk in AF have important weaknesses. When Lip et al. applied nine different RSMs to a real-world cohort of 1084 patients drawn from the Euro Heart Survey for AF, they found that the c-statistic (a measure of predictive ability) was uniformly low, varying from 0.561 (CHADS2 index) to a maximum of 0.638 (Framingham index) [78]. As a reflection of this lack of discriminatory power, a large proportion of patients were classified as intermediate risk (from 12.2% using the AFI 1994 rule, to 61.9% using the CHADS2 index); this is the least useful category for clinical decision making. In contrast, an ideal risk prediction tool would dichotomize patients into truly low and truly high risk groups (Figure 6). In addition, the ideal RSM should:

- Be derived by a methodologically rigorous process
- Be validated in a representative clinical population
- Be subject to formal impact analysis to establish utility in clinical practice

So far, no RSM has fulfilled all four of these requirements.
A recent derivative of the CHADS2 RSM is the CHA2DS2-VA2Sc index, which incorporates additional clinical variables (female gender, history of vascular disease – prior myocardial infarction, peripheral arterial disease and aortic plaque) and splits the binary age variable into a ternary one (assigning zero points to age <65, 1 point between 65 and 74 and two points for age ≥75). In the validation population, this index categorized 9% of patients at low risk (0% stroke risk per year) and 15% at intermediate risk (0.6% per year). Although recognized and advocated as a valid RSM in the recent European Society of Cardiology guidelines, the CHA2DS2-VASc index does not really address the fundamental shortcoming of all RSMs, as described earlier (Figure 6).

Treatment-related harm: estimation of bleeding risk

RSMs for bleeding risk have similarly been developed, for example the HEMORR2HAGES score (Table 4) [79]. More recently, a simpler schema with a shorter acronym, HAS-BLED, has been proposed; it incorporates many of the same risk factors as HEMORR2HAGES. This HAS-BLED score (Table 5) [80] was derived from 3978 patients in the Euro Heart Survey on AF with complete follow-up. It has been validated in the SPORTIF III and V cohorts [81], together comprising 7329 patients, and appears to perform as well or better than the HEMORR2HAGES score (overall c-statistic for HAS-BLED: 0.72 [95% CI: 0.65–0.79] versus HEMORR2HAGES: 0.66 [95% CI: 0.57–0.74]).

### Table 4. Bleeding risk stratification models: HEMORR2HAGES score.

<table>
<thead>
<tr>
<th>HEMORR2HAGES risk factors (score)</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic (1) or renal disease (1)</td>
<td>Hepatic disease: cirrhosis, twofold or greater elevation of AST or APT or albumin &lt;3.6 g/dlBP. Renal insufficiency: creatinine clearance &lt;30 ml/min</td>
</tr>
<tr>
<td>Ethanol use (1)</td>
<td>History of alcohol abuse, recent hospitalization for alcohol-related illness and worsening liver disease</td>
</tr>
<tr>
<td>Malignancy (1)</td>
<td>Recent metastatic cancer</td>
</tr>
<tr>
<td>Age &gt;75 (1)</td>
<td>Calculated from birth date</td>
</tr>
<tr>
<td>Reduced platelet count (1) or function (1)</td>
<td>Platelets &lt;75,000 Schedule use of antiplatelet therapy (e.g., daily aspirin) or NSAID therapy or blood dyscrasia</td>
</tr>
<tr>
<td>Re-bleeding (2)</td>
<td>Prior hospitalization bleeding</td>
</tr>
<tr>
<td>Hypertension, uncontrolled (1)</td>
<td>Blood pressure not currently in control: most recent systolic bp &gt;160 Torr</td>
</tr>
<tr>
<td>Anemia (1)</td>
<td>Most recent hematocrit &lt;30 or hemoglobin &lt;10 g/dl</td>
</tr>
<tr>
<td>Genetic factors (1)</td>
<td>CYP2C9<em>2 and/or CYP2C9</em>3</td>
</tr>
<tr>
<td>Elevated risk of fall including neuropsychiatric disease (1)</td>
<td>Alzheimer’s dementia, Parkinson’s disease, schizophrenia or any condition predisposing to repeated falls</td>
</tr>
<tr>
<td>Stroke (1)</td>
<td>Prior ischemic stroke or brain infarct detected by brain imaging</td>
</tr>
</tbody>
</table>

Data taken from [78].

### Table 5. Bleeding risk stratification models: HAS-BLED score.

<table>
<thead>
<tr>
<th>Letter</th>
<th>Feature</th>
<th>Points</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension†</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal† and liver function† (1 point each)</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding†</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs†</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (e.g., age &gt;65 years)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol (1 point each)</td>
<td>1/2</td>
<td>1/2</td>
</tr>
</tbody>
</table>

Maximum 9 points

†Defined as systolic blood pressure >160 mmHg.
††Defined as chronic dialysis or renal transplantation or serum creatinine ≥200 µmol/l.
‡Defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin >2× ULN in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3× ULN).
¶Refers to previous bleeding history and/or predisposition to bleeding (e.g., bleeding diathesis and anemia).
#Refers to unstable/high INRs or poor time-in-therapeutic window (e.g., <60%).
†††Refers to concomitant use of drugs such as antiplatelet agents, non-steroidal anti-inflammatory drugs or alcohol abuse.
INR: International normalized ratio; ULN: Upper limit of normal.
Summary

In the future, there will undoubtedly be iterative refinements to clinical RSMs for predicting stroke. Overall, however, it seems unlikely that risk indices relying entirely on clinical variables will be able to optimally segregate patients into truly low and high stroke risk groups. The addition of variables derived from imaging studies (e.g., left ventricular ejection fraction indices of left atrial size), electrocardiography or biochemical measurements (e.g., B-type natriuretic peptide) to clinical variables may help to improve risk prediction, but this will be at the cost of complexity and decreasing the general applicability. It remains to be seen whether such hybrid RSMs will be developed and validated in a large population and gain general acceptance. Application of RSMs for bleeding risk will also help guide patient selection for oral VKAs and antiplatelet therapy; however, these will need to be re-validated once novel oral anticoagulant agents enter more widespread clinical use.

Conclusion & future perspective

The prevalence of AF continues to rise, and stroke prophylaxis in these patients will inevitably become more important. Currently, there is robust evidence supporting the use of oral VKAs for this purpose. Two of the newer oral anticoagulants, dabigatran and rivaroxaban, also appear efficacious. They also seem safer and more convenient than oral VKA. In the near future, these agents will likely replace warfarin, at least in part. Percutaneous LAA occlusion devices, and surgical LAA exclusion procedures also appear effective, but general application will be limited by their invasive nature and cost considerations. Finally, neither AADs nor AF ablation appear effective in lowering stroke risk. If more effective methods of abolishing AF and keeping patients in sinus rhythm could be developed, it is possible that stroke risk would also be lower; in the near term however, this is not likely.

Executive summary

Anticoagulation strategies

- Nonvalvular atrial fibrillation (AF) increases the risk of stroke by approximately fivefold.
- Oral vitamin K antagonists (warfarin) can reduce the risk by approximately 50–70%, but efficacy and risks are associated with the time-in-therapeutic range; this is approximately 40–65% in most centers.
- Newer oral agents under development principally target thrombin or factor Xa of the coagulation cascade, and do not need monitoring of the international normalized ratio.
- Use of these novel oral anticoagulants is starting to enter clinical practice, although there is some uncertainty with respect to their exact place in relation to current therapy/oral vitamin K antagonists.

Left atrial appendage closure strategies

- The principle mechanism by which AF increases stroke risk is by cardioembolism of left atrial appendage (LAA) thrombus.
- Surgical and percutaneous LAA exclusion are both feasible.
- Surgical exclusion of the LAA may be effective, but efficacy is likely technique and operator dependent and the evidence is not conclusive so far.
- Percutaneous closure of the LAA can be achieved by a variety of methods; the best developed so far is the Watchman device, which has received conditional US FDA approval for stroke prophylaxis in nonvalvular AF.

Rhythm control strategies

- Maintenance of sinus rhythm might logically be expected to reduce the risk of AF-associated stroke.
- However, current techniques for restoring and maintaining sinus rhythm (antiarrhythmic drugs, surgical or percutaneous modification of AF triggers and the atrial substrate) have poor long-term efficacy.
- So far, such therapies cannot be recommended for reducing stroke risk.

Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest


This large study including 17,974 patients provides a population estimate of atrial fibrillation (AF) burden, and considers the implications of changing population demographics on AF burden.


This seminal analysis of the five major randomized trials of warfarin for primary prevention of stroke in AF demonstrated that warfarin consistently decreased the risk of stroke.


Summarizes the data for surgical and percutaneous left atrial appendage (LAA) exclusion for stroke prophylaxis in AF.


North American guidelines on the use of antithrombotic therapy in AF.


review: clinical trial outcomes


45 European guidelines on AF management.


47 North American guidelines on AF management.


53 Of historical interest, this paper described the feasibility of amputation of the atrial appendages in dogs.


59 Concise review of the structure, function and role of the LAA in thromboembolism.


Current & emerging therapies for stroke prophylaxis in atrial fibrillation

Review: Clinical Trial Outcomes


