Stroke Risk and Antithrombotic Strategies in Atrial Fibrillation

Caroline Medi, BMed, FRACP; Graeme J. Hankey, MBBS, MD, FRCP(Lond), FRCP(Edin); Saul B. Freedman, MBBS, PhD, FRACP, FACC

Background and Purpose—Although the stroke rate associated with atrial fibrillation has declined over the last 10 years, the emerging atrial fibrillation epidemic threatens to increase the incidence of cardioembolic stroke.

Summary of Review—Oral anticoagulants are superior antithrombotic agents but are underused due to fear of bleeding and uncertainty about which patients will benefit. Individualized decisions on antithrombotic therapy require balancing the competing risks of thromboembolism and bleeding. The CHADS2 (Congestive heart failure, Hypertension, Age >75 years, and Diabetes mellitus, and 2 points for prior Stroke/transient ischemic attack) score and other schemes provide an estimate of thromboembolic risk; however, the external validity of these estimates in the context of well-controlled risk factors, or a hypercoagulable state, is uncertain. Moreover, it is very difficult to estimate bleeding risk. Recent studies highlight the need for meticulous international normalized ratio control to achieve optimal outcomes hampered by the high bleeding risk during oral anticoagulant inception and other limitations of warfarin. Dabigatran is at least as efficacious as warfarin in preventing stroke and systemic embolism for patients in whom the risk of thromboembolism outweighs bleeding risk. In addition, the results of ongoing trials evaluating alternative anticoagulants such as oral anti-Xa agents are awaited. In this review, we discuss emerging therapies including available and completed trials of direct antithrombins and anti-Xa agents, including ximelagatran, idraparinaux, and dabigatran; and new device therapies including left atrial appendage occlusion devices.

Conclusions—in light of these promising new therapies, it is likely that atrial fibrillation thromboembolism guidelines will need to be rewritten and frequently updated. (Stroke. 2010;41:2705-2713.)

Key Words: anticoagulation ■ aspirin ■ atrial fibrillation ■ dabigatran ■ stroke prevention ■ warfarin

Atrial fibrillation (AF) is associated with twice the mortality of age-matched controls and 10-fold higher mortality within 4 months of diagnosis.1 In the last 25 years, the age- and sex-adjusted annual incidence of AF has increased by 12.6%.2 Although the incidence of stroke associated with AF has declined in the last 5 to 10 years, concurrent with increased oral anticoagulant (OAC) use and better blood pressure control,3 the rising incidence and increasing age of the population is projected to increase stroke burden from 38 million disability-affected life-years in 1990 to 60 million disability-affected life-years by 2020.4

The past year has seen the publication of results of some of the largest and arguably most significant clinical trials of antithrombotic and other strategies to prevent stroke among patients with AF. In this review, we discuss these results in the context of current best evidence and examine how they may impact on the prophylactic antithrombotic management of patients with AF.

Thromboembolism in AF

Thrombus Formation in AF

AF results in a loss of organized atrial contraction and is associated with stasis in the left atrial appendage (LAA), reduced LAA flow velocities, and thrombus formation.5 When AF is of >2 days’ duration, atrial thrombi may be seen in up to 14% patients on transesophageal echocardiography ranging from 0.2 to 4.2 cm in size.6 Embolic strokes caused by AF are typically larger, more commonly disabling and fatal, and occur at more advanced age compared with strokes occurring in sinus rhythm.7 However, up to 25% of AF-associated strokes originate from alternate sources, including the left ventricle, aortic arch, extracranial arteries, and in situ disease of the intracranial cerebral arteries.8

Assessing Thromboembolic Risk in Nonvalvular AF

Patients with AF and rheumatic mitral valve disease have a high risk of stroke, and OACs are indicated.9 In nonvalvular AF, the annual stroke risk on aspirin is similar for paroxysmal (3.2%) and permanent (3.3%) AF,10 so recommendations on antithrombotic therapy pertain equally to both. The stroke risk with atrial flutter is intermediate between sinus rhythm and AF11; however, up to 75% have coexistent AF or later develop it.12 Therefore, guideline recommendations are similar.13 For patients with lone AF (<60 years without risk...
Table 1. Annual Risk of Stroke With Nonvalvular AF Not Treated With Anticoagulation (With 95% CIs) According to the CHADS2 Score*18,19

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Stroke Risk (%)</th>
<th>95% CI</th>
<th>Patients (n=1733)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
<td>1.2–3.0</td>
<td>120</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
<td>2.0–3.8</td>
<td>463</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>3.1–5.1</td>
<td>523</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
<td>4.6–7.3</td>
<td>337</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
<td>6.3–11.1</td>
<td>220</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
<td>8.2–17.5</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
<td>10.5–27.4</td>
<td>5</td>
</tr>
</tbody>
</table>

*The adjusted annual stroke rate was derived from multivariate analysis assuming no aspirin use.

Factors or structural heart disease), the cumulative risk of stroke over 15 years is very low (approximately 1.3%).14

In patients with nonvalvular AF, the strongest independent predictor of stroke is prior stroke/transient ischemic attack (relative risk [RR], 1.9 to 3.7).15 Increasing the annual stroke risk to 12%/year with no antithrombotic therapy and 10%/year on aspirin.16 Age increases the relative risk of stroke/systemic embolism by 1.4 with each decade.17 Other independent risk factors include hypertension,10 diabetes mellitus (RR, 1.7), and recent cardiac failure or moderate–severely impaired left ventricular ejection fraction (RR, 1.4).17

The CHADS2 Index is a widely used risk scheme in AF, allocating 1 point for each risk factor of Congestive heart failure, Hypertension, Age >75 years, and Diabetes mellitus, and 2 points for prior Stroke/transient ischemic attack18,19 (Table 1). Based on risk factors, annual stroke risk on aspirin may be calculated to select patients who would benefit from OAC. The CHADS2 and other risk stratification schemes have only limited ability to accurately predict thromboembolism in patients with AF20. A comparison of 5 risk stratification schemes to predict thromboembolism in a large community-based cohort of 13,559 adults with AF revealed that the risk schemes had only fair discriminating ability with C-statistics ranging from 0.56 to 0.62 (0.58 for the CHADS2 score; Table 2).20

These risk stratification schemes provide an estimate of risk and do not take into account the severity and duration of risk factors. The stroke risk at 85 years is significantly higher than at 75 years, yet this is not taken into account in the CHADS2 calculation. Similarly, poorly controlled diabetes mellitus, hypertension, and heart failure probably pose an increased risk relative to well-controlled disease. Large left atrial size and spontaneous echo contrast are also omitted. It is uncertain whether scores like CHADS2 remain externally valid now with better risk factor control; it is noteworthy that in recent trials, stroke risk for CHADS2=2 has diminished.22

The revised American College of Cardiology/American Heart Association/European Society of Cardiology guidelines endorse either aspirin or warfarin in patients with CHADS2=1.13 Clinical features that would favor OAC use over aspirin include moderate–severe left ventricular dysfunction, LAA thrombus/spontaneous echo contrast, reduced velocities within the LAA, and aortic atheroma on transesophageal echocardiogram.23

Table 2. Three Common Schemes of Stratifying Risk of Stroke Among Patients in AF21

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>ACC/AHA/ESC Guideline</th>
<th>ACCP Practice Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure—1 point*</td>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Hypertension—1 point‡</td>
<td>Prior thromboembolism†</td>
<td>Prior thromboembolism†</td>
</tr>
<tr>
<td>Age &gt;75 years—1 point</td>
<td>≥2 moderate risk features</td>
<td>≥2 moderate risk features</td>
</tr>
<tr>
<td>Diabetes—1 point</td>
<td>Intermediate risk</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Stroke/TIA—2 points</td>
<td>Age &gt;75 years</td>
<td>Age &gt;75 years</td>
</tr>
<tr>
<td>Moderate risk: 1 point</td>
<td>Heart failure§</td>
<td>Heart failure§</td>
</tr>
<tr>
<td>Low risk: 0 points</td>
<td>Hypertension‡</td>
<td>History of hypertension ‡</td>
</tr>
<tr>
<td>Moderate risk: 2 points</td>
<td>Diabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;35% or fractional shortening &lt;25%</td>
<td>Moderately to severely impaired left ventricular systolic function¶</td>
<td>Low risk**</td>
</tr>
</tbody>
</table>

*Recent heart failure exacerbation was used in the original stratification but subsequently any prior or current heart failure has supplanted.

†Prior stroke, TIA, or systemic embolism.

‡A history of hypertension not specifically defined.

§Not clear whether history of heart failure, recent heart failure, or current heart failure.

¶In previous studies, moderate risk was typically defined as CHADS2 scores of 1 or 2. The current definition makes the 3 schemes very similar.

**Echocardiographic parameters 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 categorized as moderate risk. Antithrombotic therapy with either warfarin or aspirin is reasonable depending on bleeding risks, ability to safely sustain anticoagulation, and patient preferences.

ACC/AHA/ESC indicates American College of Cardiology/American Heart Association/European Society of Cardiology; ACCP, American College of Chest Physicians; TIA, transient ischemic attack.
Assessing Risk of Bleeding With OAC

In clinical studies with careful monitoring of anticoagulant intensity, treatment with OAC increases the risk of major bleeding by 0.3 to 0.5%/year, from approximately 1%/year to 1.4%/year, and the risk of intracranial hemorrhage by 0.2%/year compared with patients without OAC. However, higher (but variable) rates have been reported in patients on OAC in clinical routine practice. “Real-life” patients are older with less well-regulated anticoagulation therapy, and the average annual rate of major hemorrhage is 1% to 5% varying with intensity of anticoagulation and age.

Major risk factors for bleeding with OAC include a concomitant bleeding tendency (eg, recent hemorrhage, uncontrolled anticoagulation, liver and kidney disease, the concomitant use of aspirin and nonsteroidal anti-inflammatory drugs), uncontrolled hypertension, binge drinking, ethnicity/race, and increasing age.

Chronic renal disease results in substantial changes in hemostasis with the paradox that patients in all stages of chronic renal disease, but especially with end-stage renal disease, have both a prothrombotic state predisposing to high risk for thromboembolism and coagulopathy with an increased tendency for bleeding. Although oral anticoagulation is the treatment of choice for AF, its use in patients with chronic renal disease is reported only in limited studies, all in patients on hemodialysis, and is associated with a markedly increased rate of bleeding compared with patients without chronic kidney disease.

There are ethnic and racial differences in risk of warfarin-related intracranial hemorrhage that should be taken into consideration. In a retrospective analysis, the hazard ratio for intracranial hemorrhage was 4.06 for Asians (95% CI, 2.47 to 6.65), 2.06 for Hispanics (95% CI, 1.31 to 3.24), and 2.04 for blacks (95% CI, 1.25 to 3.35) compared with whites. There are also ethnic differences in the prevalence of certain polymorphisms in genes that influence warfarin pharmacokinetics and pharmacodynamics such as cytochrome P450 2CY and vitamin K epoxide reductase. Asians generally require a lower warfarin dose to maintain a target international normalized ratio with whites intermediate and blacks requiring the highest daily dose. In patients on warfarin, the variant CYP2C9 genotype conferred an increased risk for major hemorrhage (hazard ratio, 3.0; 95% CI, 1.1 to 8.0).

Patients at high risk for falls are at even higher risk for ischemic stroke associated with AF (13.7 per 100 patient-years), yet also are at increased risk of intracranial hemorrhage compared with other patients (2.8 versus 1 per 100 patient-years). Prescription of warfarin does not affect the incidence rate of intracranial hemorrhage but increases the severity of the hemorrhagic events with a higher 30-day mortality in patients on warfarin (51.8% versus 33.6% for those without warfarin; \( P=0.007 \)).

Cognitive dysfunction is common in elderly patients with AF and even mild cognitive impairment is related to less effective anticoagulation and more vascular and bleeding events. Leukoaraiosis (hazard ratio, 2.7; 95% CI, 1.4 to 5.3), age >65 years (hazard ratio, 1.9; 95% CI, 1.0 to 3.4), and increasing international normalized ratio (INR; hazard ratio, 1.37 for each 0.5-U increase in INR) were the independent predictors of all anticoagulation-related hemorrhages in 651 anticoagulated patients with nondisabling cerebral ischemia in the Stroke Prevention In Reversible Ischemia Trial (SPIRIT).

Cerebral microbleeds are indicative of a microangiopathy that predisposes to small bleeds in the brain and may be detected by turbo spin-weighted gradient-recalled echo MRI. Although patients with cerebral microbleeds are older and have more leukoaraiosis, the impact of warfarin treatment on cerebral microbleeds is still controversial.

Management of antithrombotic therapy after serious hemorrhagic complications such as intracranial hemorrhage is controversial. After intracranial hemorrhage, resumption of anticoagulation should be avoided unless the patient is at very high risk of thromboembolism and low risk of recurrent hemorrhage. Based on current guidelines, warfarin may be restarted after a minimum of 7 to 14 days after the hemorrhagic event; however, this is based on Class IV evidence only.

Classic Pharmacologic Therapies

Warfarin or Antiplatelets (Aspirin Alone, or Aspirin/Clopidogrel)

OACs have consistently been shown to be superior to placebo and antiplatelet agents in secondary prevention and in primary prevention in patients at moderate–high risk of stroke (CHADS2 score ≥2; Figure). A meta-analysis comparing adjusted-dose warfarin with control demonstrated a 64% reduction in stroke RR with absolute risk reductions of 2.7%/year for primary prevention and 8.4%/year for secondary prevention.

A meta-analysis of antiplatelet therapy compared with placebo showed that antiplatelet therapy was associated with a modest reduction in the incidence of stroke (relative risk reduction, 22%) by reducing nondisabling noncardioembolic strokes. When anticoagulant therapy was compared with warfarin, a significantly greater reduction in stroke was observed with warfarin (relative risk reduction, 39%).

The superior efficacy seen with warfarin is accompanied by increased major bleeding (RR, 1.7), but aspirin is less effective (absolute risk reduction, 1.5% and 2.5%/year for primary and secondary prevention, respectively).
1000 patients with AF for 1 year with OAC rather than aspirin would prevent 23 ischemic strokes at the same time as causing 9 major bleeds. The net benefit of OAC is therefore most prominent in those with high stroke risk.44

The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W) trial comparing warfarin (target INR 2 to 3) with aspirin (75 to 100 mg) and clopidogrel (75 mg) was prematurely stopped after warfarin demonstrated fewer major vascular events45 with comparable bleeding. The major advantage of warfarin was fewer strokes (1.40%/year versus 2.39%/year, \(P = 0.001\)). Most patients were previously established on warfarin, and although not a prespecified subgroup, in patients already receiving warfarin at study entry, warfarin was superior to aspirin/clopidogrel. In warfarin-naive patients, the 2 groups were similar in efficacy (RR, 1.3; 0.8 to 1.9) with a trend to less major bleeding with dual antiplatelet therapy (RR, 0.6; 0.3 to 1.1), highlighting the problems associated with warfarin inception. In patients with contraindications to, or non-compliance with, OAC or its monitoring, ACTIVE-A compared aspirin with aspirin/clopidogrel in patients with AF with \(\geq 1\) risk factor for stroke.46 Dual antiplatelet therapy resulted in a reduction of the combined end point of stroke, myocardial infarction, systemic embolism, and vascular death from 7.6% to 6.8% per year (RR, 0.89; 95% CI, 0.81 to 0.98), primarily driven by a reduction in stroke, but with a significant increase in major bleeding from 1.3%/year to 2%/year.

**Emerging Pharmacologic Therapies**

**Direct Thrombin Inhibitors**

The direct thrombin inhibitor ximelagatran was 1 of the first oral anticoagulants to be evaluated as a potential warfarin alternative but was later withdrawn due to rare and potentially fatal hepatotoxicity.47 The Atrial fibrillation trial of Monitored, Adjusted Dose vitamin K antagonist, comparing Efficacy and safety with Unadjusted SanOrg 34006/idraparinux (AMADEUS) trial comparing idraparinux (subcutaneously injected factor Xa inhibitor) with warfarin was stopped early due to excess bleeding.48 Dabigatran is a congenor of ximelagatran without hepatotoxicity, which has undergone extensive trialing. It also requires no anticoagulant monitoring and has few interactions but requires twice-a-day dosage and effects cannot be acutely reversed with certainty.

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) study, a total of 18 113 patients with nonvalvular AF and at least 1 risk factor for stroke were randomized to low-dose (110 mg twice daily) or high-dose dabigatran (150 mg twice daily) or to adjusted-dose warfarin (INR, 2 to 3).49 After a median follow-up of 2.0 years, the rates of the primary outcome, systemic embolism, or stroke (including hemorrhagic stroke) were similar among patients assigned 110 mg dabigatran twice daily and warfarin (RR, 0.91; 95% CI, 0.74 to 1.11; \(P < 0.001\) for noninferiority) and significantly lower among patients assigned 150 mg dabigatran twice daily (RR, 0.66; 95% CI, 0.53 to 0.82; \(P < 0.001\) for superiority).

Compared with warfarin, the annual rate of major bleeding was lower among patients assigned 110 mg dabigatran twice daily (RR, 0.80; 95% CI, 0.69 to 0.93) and similar among patients assigned 150 mg dabigatran twice daily (RR, 0.93; 95% CI, 0.81 to 1.07). Gastrointestinal bleeding was however significantly increased by dabigatran compared with warfarin. Compared with warfarin (0.38% per year), the rates of hemorrhagic stroke were lower with 110 mg twice daily of dabigatran (0.12% per year; RR, 0.31; 95% CI, 0.17 to 0.56) and 150 mg twice daily of dabigatran (0.10% per year; RR, 0.26; 95% CI, 0.14 to 0.49).

Rates of myocardial infarction were significantly more common with dabigatran (0.72% and 0.74% with 110 mg and 150 mg dabigatran, respectively) than with warfarin (0.53% with warfarin), but the mechanism and significance remain to be ascertained. Rates of dyspepsia (including abdominal pain) were higher with dabigatran (11.8% with 110 mg, 11.3% with 150 mg) compared with warfarin (5.8%), presumably caused by the tataric acid content of the dabigatran etexilate capsule, and this contributed to the greater rate of dropout over 2 years with dabigatran (approximately 21%) than with warfarin (16.6%). The rates of the combined clinical outcome (major vascular events, major bleeding, and death) were 7.64% per year with warfarin and 7.09% per year with 110 mg dabigatran (RR with dabigatran, 0.92; 95% CI, 0.84 to 1.02; \(P = 0.10\)) and 6.91% per year with 150 mg dabigatran (RR, 0.91; 95% CI, 0.82 to 1.00; \(P = 0.04\)). The results were consistent among warfarin-experienced and -naive patients, indicating it would be safe to switch from warfarin to dabigatran. Although dabigatran is currently under evaluation, on September 20 this year it received a unanimous recommendation by the FDA panel for preventing stroke in AF.

RandomizEd Dabigatran Eteixilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel (REDEEM) trial was a bleeding safety trial, which entered 1861 patients presenting after acute ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction with at least 1 cardiovascular risk factor. They were randomized to placebo or to dabigatran at 1 of 4 dosages (50 mg twice daily, 75 mg twice daily, 110 mg twice daily, and 150 mg twice daily) starting within a few weeks of the acute coronary syndrome and continuing for 6 months. International Society on Thrombosis and Haemostasis (ISTH) major bleeding complications increased with higher dosing, from 0.5% (placebo) to 2.0% (110 mg twice-daily dabigatran) and 1.2% (150 mg twice-daily dabigatran).50

There are a number of promising future anticoagulants, particularly the orally effective anti-Xa drugs, currently under assessment in large ongoing clinical trials (Table 3). A trial of 1 of these drugs, apixaban (Apixaban versus Acetylsalicylic Acid to Prevent Strokes [AVERRROES] trial), comparing this drug with aspirin in patients intolerant of or unsuitable for warfarin was recently stopped early because of clear evidence of a clinically important reduction in stroke and systemic embolism with a reported acceptable safety profile compared with aspirin.51 It is probable that results with some of these drugs will require us to re-evaluate guidelines for antithrombotic prophylaxis in AF. A comparison of old and new pharmacological therapies and percutaneous closure devices in low- and high-risk CHADS2 patients is shown in Table 4.
Table 3. Current Trials of Anticoagulant Treatments in the Prevention of Stroke in Patients With AF

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Size, No.</th>
<th>Patients</th>
<th>Interventions</th>
<th>Outcome</th>
<th>Results Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET-AF</td>
<td>14 266</td>
<td>AF plus ≥2 risk factors for stroke</td>
<td>Rivaroxaban 20 mg daily plus warfarin placebo versus warfarin (INR, 2.0 to 3.0) plus rivaroxaban placebo</td>
<td>Stroke or noncentral nervous system embolism; clinically relevant bleeding</td>
<td>2010</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>15 000</td>
<td>AF plus ≥1 risk factor for stroke</td>
<td>Apixaban 5 mg twice a day plus warfarin placebo versus warfarin (INR, 2.0 to 3.0) plus apixaban placebo</td>
<td>Stroke or noncentral nervous system embolism; clinically relevant bleeding</td>
<td>2010</td>
</tr>
<tr>
<td>AVERROES</td>
<td>5600</td>
<td>AF plus ≥1 risk factor for stroke, 40% warfarin naïve</td>
<td>Apixaban 5 mg twice a day versus aspirin</td>
<td>Stroke or noncentral nervous system embolism; clinically relevant bleeding</td>
<td>Stopped early for efficacy June 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 versus warfarin (INR, 2.0 to 3.0) plus edoxaban placebo</td>
<td>Stroke or noncentral nervous system embolism; clinically relevant bleeding</td>
<td>2012</td>
</tr>
<tr>
<td>AZD0837 Trial</td>
<td>250</td>
<td>AF plus ≥1 risk factor for stroke</td>
<td>AZD0837 150 mg twice a day or AZD0837 350 mg twice a day versus warfarin (INR, 2.0 to 3.0)</td>
<td>Stroke or noncentral nervous system embolism; clinically relevant bleeding</td>
<td>2010</td>
</tr>
</tbody>
</table>

ROCKET-AF indicates Randomized, Double-Blind Study Comparing Once Daily Oral Rivaroxaban With Adjusted-Dose Oral Warfarin for the Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation; ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; ENGAGE-AF TIMI-48, Global Study to Assess the Safety and Effectiveness of DU-176b vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation; AZD0837 is a prodrug converted to a selective and reversible direct thrombin inhibitor (AR-H067637).

Novel Nonpharmacologic Approaches

LAA Closure Devices

In PROTECTion in Patients With Atrial Fibrillation (PROTECT-AF), a percutaneous closure device occluding the LAA (WATCHMAN) was compared with conventional treatment with warfarin in patients with AF and CHADS2 ≥1.52 Patients were anticoagulated with warfarin in the postimplantation period and switched to aspirin/clopidogrel for 6 months and then indefinite aspirin alone if transesophageal echocardiogram at 45 days postimplantation confirmed LAA closure. The device was noninferior to warfarin in the primary efficacy outcome (stroke, systemic emboli, cardiovascular, or other death) with fewer hemorrhagic strokes and 90% patients able to stop warfarin. However, adverse events (combining major bleeding, pericardial effusion, and device embolization) were higher in the device group, largely driven by the increased incidence of pericardial effusion. Although this device may have a role in thromboprophylaxis in those at high stroke risk with contraindications to warfarin, it will not prevent embolism originating outside the atrial appendage, and its long-term efficacy is uncertain.

OAC in the Elderly

Elderly patients show a greatly increased major hemorrhage risk during OAC intake, especially if >80 years or CHADS2 ≥3.34 The annual risk of major bleeding in patients >80 years who are not enrolled in clinical trials approximates 2%.53 Elderly patients with AF derive greater benefit from OAC at the expense of increased major hemorrhage. Aiming for an INR at the lower end of the therapeutic range (2.0 to 2.5) may be a reasonable benefit/risk tradeoff for primary prevention in elderly patients with nonvalvular AF. The results from Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) and other small randomized studies54 indicate that highly select, low-risk very elderly patients do benefit from OAC use, but these results may not be generalizable due to high rates of aspirin/OAC use before trial enrollment in BAFTA.55 In the absence of clear evidence, the pragmatic approach would be to prescribe aspirin or possibly low-dose dabigatran in the very elderly with a frank discussion about safety/efficacy tradeoff.

Impact of Anticoagulation Control on Outcomes With OAC

If INR is subtherapeutic >40% of the time, there is little benefit of OAC over antiplatelet therapy.56 In patients with nonvalvular AF, anticoagulation that results in an INR of ≥2.0 reduces the disability from stroke and mortality57,58. In patients presenting with stroke who were taking warfarin, an INR of <2.0 at admission, as compared with an INR of ≥2.0, independently increased the odds of a severe stroke (OR, 1.9; 95% CI, 1.1 to 3.4) and 30-day mortality (hazard ratio, 3.4; 95% CI, 1.1 to 10.1). An INR of 1.5 to 1.9 at admission was associated with a mortality rate similar to that for an INR of <1.5. The Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) trials showed that patients with poor INR control (<60% in therapeutic range) had a 2%/year higher absolute mortality than patients with moderate–good INR control and higher rates of stroke/systemic embolization, myocardial infarction, and major

### Table 3. Current Trials of Anticoagulant Treatments in the Prevention of Stroke in Patients With AF

<table>
<thead>
<tr>
<th>Design</th>
<th>Study Size, No.</th>
<th>Patients</th>
<th>Interventions</th>
<th>Outcome</th>
<th>Results Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET-AF</td>
<td>14 266</td>
<td>AF plus ≥2 risk factors for stroke</td>
<td>Rivaroxaban 20 mg daily plus warfarin placebo versus warfarin (INR, 2.0 to 3.0) plus rivaroxaban placebo</td>
<td>Stroke or noncentral nervous system embolism; clinically relevant bleeding</td>
<td>2010</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>15 000</td>
<td>AF plus ≥1 risk factor for stroke</td>
<td>Apixaban 5 mg twice a day plus warfarin placebo versus warfarin (INR, 2.0 to 3.0) plus apixaban placebo</td>
<td>Stroke or noncentral nervous system embolism; clinically relevant bleeding</td>
<td>2010</td>
</tr>
<tr>
<td>AVERROES</td>
<td>5600</td>
<td>AF plus ≥1 risk factor for stroke, 40% warfarin naïve</td>
<td>Apixaban 5 mg twice a day versus aspirin</td>
<td>Stroke or noncentral nervous system embolism; clinically relevant bleeding</td>
<td>Stopped early for efficacy June 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 versus warfarin (INR, 2.0 to 3.0) plus edoxaban placebo</td>
<td>Stroke or noncentral nervous system embolism; clinically relevant bleeding</td>
<td>2012</td>
</tr>
<tr>
<td>AZD0837 Trial</td>
<td>250</td>
<td>AF plus ≥1 risk factor for stroke</td>
<td>AZD0837 150 mg twice a day or AZD0837 350 mg twice a day versus warfarin (INR, 2.0 to 3.0)</td>
<td>Stroke or noncentral nervous system embolism; clinically relevant bleeding</td>
<td>2010</td>
</tr>
</tbody>
</table>

ROCKET-AF indicates Randomized, Double-Blind Study Comparing Once Daily Oral Rivaroxaban With Adjusted-Dose Oral Warfarin for the Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation; ARISTOTLE, Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; ENGAGE-AF TIMI-48, Global Study to Assess the Safety and Effectiveness of DU-176b vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation; AZD0837 is a prodrug converted to a selective and reversible direct thrombin inhibitor (AR-H067637).
bleeding.\textsuperscript{59} This analysis highlights the difficulty of achieving good INR control in clinical practice; even in the stringent clinical trial setting, two thirds did not have a therapeutic INR $>75\%$ of the time. In “real life,” missed and additional doses are frequent, resulting in over- and underanticoagulation.

The difficulty in predicting OAC dose, and who will have suboptimal INR control, makes the direct antithrombins, and anti-Xa agents, which have few drug or food interactions and do not require monitoring, more appealing. On the other hand, twice-a-day dosage may reduce compliance, which cannot be checked by a readily available blood test.

The Treatment Gap in AF

In patients presenting with ischemic stroke, prior or newly diagnosed AF occurs in 15\% to 38\%. Patients with known AF not on appropriate OAC account for a significant burden of disability and mortality. In 1 study, one third of patients were on no antithrombotic therapy, one third were on antiplatelet treatment, and one fourth were on warfarin with subtherapeutic INR.\textsuperscript{60} The reasons for undertreatment are complex but include lack of knowledge about trials/guidelines, perceived “potential contraindications,” fear of bleeding, and inconvenience of monitoring. Perceived lower risk in patients with paroxysmal AF and CHADS$_2 \geq 2$ leads to a systematic undertreatment in high-risk patients.\textsuperscript{61}

### Anticoagulation Management in Specific Clinical Contexts

#### Anticoagulation Before and After Cardioversion

Thrombotic complications are minimized with OAC therapy given 3 to 4 weeks before and after cardioversion.\textsuperscript{62} Thrombus in the LAA has been identified on transesophageal echocardiogram after AF episodes of relatively short duration (<48 hours).\textsuperscript{63} Performance of transesophageal echocardiogram to exclude left atrial thrombus before cardioversion, and anticoagulating with enoxaparin over unfractionated heparin, has been associated with lower bleeding rates than the conventional approach.\textsuperscript{64} After cardioversion, atrial stunning generally improves within the first few days with mechanical function returning between 1 and 4 weeks.\textsuperscript{65} This parallels the time course of thromboembolic complications seen postcardioversion.\textsuperscript{66}

#### Interruption of OAC Before and After Surgery

Patients with AF undergoing surgery have a competing problem of surgical bleeding when anticoagulated and thrombotic risk off OAC. When thrombotic risk is high (CHADS$_2 \geq 2$), minimizing duration without OAC and prescribing enoxaparin/unfractionated heparin at the earliest safe time postprocedure is an appropriate strategy. When CHADS$_2 \leq 1$, warfarin may be temporarily stopped with a low incidence of
thromboembolic and bleeding complications. Dabigatran may have a safer profile given its relatively short half-life and rapid onset of action without a transient hypercoagulable phase after resuming therapy.

**Anticoagulation After Catheter Ablation for AF**

Anticoagulation management in patients after ablation has remained challenging, due in part to uncertainty about asymptomatic AF recurrences. No prospective randomized studies are available to guide the decision of whether to stop warfarin after long-term maintenance of sinus rhythm postcatheter ablation, and the decision has largely been left to physician discretion. An international consensus document (Heart Rhythm Society, European Heart Rhythm Association, European Cardiac Arrhythmia Society) recommends OAC for a minimum of 2 months postprocedure. Thereafter, patients with CHADS$_2$ ≥2 should remain on OAC.

**Other Therapeutic Strategies to Reduce Stroke in AF**

**Antiarrhythmic Drugs and Stroke**

A rhythm over rate control strategy has not been shown to reduce the risk of stroke in atrial fibrillation. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, ischemic stroke rate was 1%/year in both rate and rhythm control groups with most strokes occurring in patients whose warfarin was stopped or subtherapeutic. In a post hoc analysis of A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patientEnTs with Atrial fibrillation/atrial flutter (ATHENA), the antiarrhythmic dronedarone was associated with less AF and reduced risk of stroke. Dronedarone also modestly reduced blood pressure and may have contributed to stroke prevention by either of these mechanisms. Dronedarone should not as yet be prescribed for stroke risk reduction until these mechanisms have been further clarified or additional studies confirm the observations.

**Aspirin and Warfarin in AF**

The addition of aspirin or other antiplatelet agents to warfarin in patients with AF who have coexistent vascular disease does not further reduce stroke or myocardial infarction rates, but major bleeding rate (including intracranial bleeds) increases as much as 3-fold with combination therapy. If aspirin is required for AF, aspirin should be stopped once INR is therapeutic.

**When Dual Antiplatelet Therapy and Warfarin Are Both Required**

Triple therapy with aspirin, clopidogrel, and OAC in patients with coronary stents and AF significantly elevates the risk of major bleeding. The challenge of simultaneously preventing systemic embolism, in-stent thrombosis, and recurrent myocardial infarction with an acceptable bleeding risk is particularly difficult, particularly early poststenting. Triple therapy after percutaneous coronary intervention/stenting is associated with increased major bleeding (0% to 21%), especially with longer duration of treatment (10.3% incidence at 6 to 12 months versus 4.6% at 1 month), whereas thromboembolic events are lower with triple therapy than warfarin and aspirin alone. The American College of Cardiology/American Heart Association/European Society of Cardiology guidelines endorse reintroduction of OAC for AF as soon as feasible postprocedure in addition to maintenance treatment with clopidogrel for a minimum of 1 month after bare metal stent, 3 to 6 months after drug-eluting stents, and 12 months in high-risk patients with warfarin monotherapy thereafter. Aspirin is recommended initially poststenting before reinstating OAC.

**Conclusions**

The current therapeutic challenge of adequately managing the burden of AF in the community is currently not met. There is a strong therapeutic need for alternative anticoagulants to OACs and a number of once or twice daily, orally administered drugs with no requirement for coagulation monitoring and dose titration are under development and in Phase III trials. After the disappointment with efficacy of dual antiplatelet therapy, and liver toxicity with ximelagatran, dabigatran was the first of these new drugs to be reported. It is important that the positive results with this drug, which may change practice, not derail the large ongoing trials of alternative anticoagulants, including oral anti-Xa and other drugs. It is hoped that other agents with equivalent or superior efficacy and safety to OAC, but without OAC inconveniences, will ultimately improve patient compliance and narrow the AF treatment gap.

**Disclosures**

G.J.H. has received honoraria for serving as a member of the executive committees of the ROCKET-AF (Johnson and Johnson), AMADEUS (Sanofi-Aventis), and BOREALIS (Sanofi-Aventis) trials; the stroke outcome adjudication committees of the RELY and AVERROES trials; the steering committee of the TRA-2P TIMI 50 trial (Scherer Plough); and the Australian Pradaxa (dabigatran) advisory board (Boehringer Ingelheim).

**References**


Stroke Risk and Antithrombotic Strategies in Atrial Fibrillation
Caroline Medi, Graeme J. Hankey and Saul B. Freedman

Stroke. 2010;41:2705-2713; originally published online October 7, 2010;
doi: 10.1161/STROKEAHA.110.589218
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/11/2705

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/