The Evolving Field of Stroke Prevention in Patients With Atrial Fibrillation

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Abstract—Vitamin K antagonists have been the standard in stroke prophylaxis in patients with atrial fibrillation for decades, but several limitations make it difficult for patients to tolerate chronic anticoagulation treatment. New drugs are under evaluation in clinical trials, including direct thrombin inhibitors and factor Xa inhibitors. Antiplatelet agents such as clopidogrel and aspirin are alternatives to warfarin for stroke prevention but have proven less efficacious in trials. The only drug to have completed a Phase III trial successfully thus far is dabigatran. The 150-mg twice-a-day dose was superior to warfarin in efficacy and similar for major bleeding, whereas the 110-mg twice-a-day dose was noninferior for efficacy and reduced major bleeding. Both doses reduced intracranial hemorrhages substantially compared with warfarin. Dabigatran-assigned patients had a higher incidence of discontinuation due to gastrointestinal symptoms. Clinically apparent myocardial infarction rates were slightly higher in the dabigatran groups than the warfarin group. Dabigatran is the first agent to show superiority over warfarin for stroke prevention in atrial fibrillation, raising the standard for newer agents. (Stroke. 2010;41[suppl 1]:S17-S20.)

Key Words: anticoagulation ■ atrial fibrillation ■ prevention

Atrial fibrillation is the most common cardiac arrhythmia with a projected incidence of 5.6 to 15.9 million people by the year 2050.1,2 The incidence increases with patient age.3 There is an increased risk of stroke; thus, adequate anticoagulation using warfarin is the cornerstone of therapy. In the next few years, the role of warfarin as the anticoagulant of choice is likely to be challenged as novel agents are developed (Figure 1).

Vitamin K Antagonists
Currently, the vitamin K antagonist warfarin is the only oral anticoagulant licensed for long-term use in patients with atrial fibrillation. Despite the effectiveness of vitamin K antagonists, they are limited by factors such as drug–drug interactions, food interactions, slow onset of action, hemorrhage, and routine anticoagulation monitoring to maintain a therapeutic international normalized ratio (INR).5 These limitations have resulted in the underuse of warfarin, leaving many at risk. New oral anticoagulants are needed that eliminate the problems of warfarin use at the same time as remaining effective for stroke prevention.

In a recent Phase IIA trial, the new vitamin K antagonist tecarfarin was evaluated in 66 individuals with atrial fibrillation at mild-to-moderate risk of stroke.7 It is not metabolized by the hepatic cytochrome P450 system and has fewer interactions than warfarin, theoretically making it easier to control. There is much evidence that patients who spend more time in the therapeutic INR range of 2.0 to 3.0 exhibit fewer clinical events.8–10 The hypothesis of the study was that the time in the therapeutic INR range on tecarfarin would exceed that on warfarin. Sixty-four patients were taking warfarin and switched to tecarfarin. Excluding the initial 3 weeks of treatment, the mean time in the therapeutic INR range was 71.4%, which is high compared with 59% on warfarin before enrollment (Figure 2).

Antiplatelet Agents
The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) program focused on the role of antiplatelet agents in stroke prevention. The ACTIVE W trial (2006) compared clopidogrel plus aspirin with warfarin and the ACTIVE A trial (2009) clopidogrel plus aspirin with aspirin alone. ACTIVE W included patients at risk for stroke and able to tolerate vitamin K antagonist therapy.11 Patients were randomly assigned to either warfarin (INR, 2.0 to 3.0; N = 3371) or 75 mg clopidogrel plus 75 to 100 mg aspirin daily (N = 3335). Warfarin reduced stroke by 42% (P = 0.001) compared with clopidogrel plus aspirin. The study was stopped early.

Patients in the double-blind ACTIVE A trial were randomly assigned to either 75 mg clopidogrel (N = 3772) or placebo (N = 3782) plus aspirin therapy.12 The addition of clopidogrel to aspirin reduced the rate of major vascular events from 7.6% to 6.8% per year (P = 0.01) compared with aspirin alone, mostly due to a reduction of strokes. However,
major bleeding was higher with clopidogrel plus aspirin compared with aspirin alone (2.0% versus 1.3% per year, respectively; \( P<0.001 \)). Aspirin plus clopidogrel proved safe for stroke prevention in patients not suited for oral anticoagulation therapy.

Warfarin was compared directly with aspirin alone for stroke prevention in the randomized Birmingham Atrial Fibrillation Treatment of the Aged study (BAFTA; 2007). In this study, 973 patients aged \( \geq 75 \) years were randomly assigned to either warfarin (INR, 2.0 to 3.0) or 75 mg aspirin daily. Warfarin patients had a mean time in the therapeutic INR range of 67% and a median INR of 2.3. Twenty-one of the 488 patients assigned to warfarin (1.6% per year) and 44 of the 485 patients assigned to aspirin (3.4% per year) had a stroke (\( P=0.003 \)). Warfarin was more effective in stroke prevention than aspirin alone.

### Oral Direct Thrombin Inhibitors

Thrombin is an attractive target for inhibition as the final effector in coagulation and a powerful propagator of fibrin. The Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) program included 2 Phase III trials examining the direct thrombin inhibitor ximelagatran (36 mg twice a day) against dose-adjusted warfarin for stroke prevention in patients with atrial fibrillation. Rates of stroke or systemic embolism in SPORTIF III were similar at 2.3% and 1.6% per year in the warfarin and ximelagatran groups, respectively (\( P=0.10 \)). The rate of major bleeding was lower, but not significantly, on ximelagatran. SPORTIF V found ximelagatran noninferior to warfarin for the primary end point (1.61% versus 1.16% per year, respectively; \( P<0.001 \)). Major bleeding was similar, but total bleeding was less with ximelagatran. The risk of hepatotoxicity resulted in a failure to approve the drug in the United States and the drug’s delicensing in Europe.

In the Randomized Evaluation of Long-term anticoagulation therapy (RE-LY) trial, 2 fixed doses of the direct thrombin inhibitor dabigatran, 110 and 150 mg twice a day, administered in a blinded fashion were compared with open-label, dose-adjusted warfarin in patients with atrial fibrillation at risk for stroke. The relative risks of stroke or systemic embolism for the 110- and 150-mg groups, respectively, were 0.91 (\( P<0.001 \) for noninferiority) and 0.66 (\( P<0.001 \) for superiority) compared with warfarin (Figure 3). The rate of major bleeding in the 110-mg group was significantly less than that in the warfarin group (2.71% versus 3.36% per year, respectively; \( P=0.003 \)), and the rate in the 150-mg group was similar (3.11% versus 3.36% per year; \( P=0.31 \)). Intracranial hemorrhages were reduced by 69% and 60% with 110 and 150 mg dabigatran, respectively, compared with warfarin (\( P<0.001 \) for both; Figure 4). Dyspepsia occurred more often in dabigatran-assigned patients, and gastrointestinal symptoms led to study-drug discontinuation in 2.2% and 2.1% of patients in the 110- and 150-mg groups, respectively, com-
pared with 0.6% in the warfarin group. Clinically manifested myocardial infarction was slightly higher in the dabigatran groups than the warfarin group (0.7% and 0.74% per year for 110 and 150 mg, respectively, versus 0.53% for warfarin; P=0.07 and 0.048, respectively). There is no need to monitor patients receiving dabigatran, and it has a rapid onset of action, advantages over warfarin that make it an easier and a potentially more economical treatment option for patients with atrial fibrillation.

### Oral Factor Xa Inhibitors

Factor Xa sits at the confluence of the extrinsic and intrinsic pathways of coagulation and is a potent multiplier of thrombin. The following factor Xa inhibitors are in development.

**Apixaban** has an absolute bioavailability of approximately 66%, reaches peak plasma concentration in 1 to 3 hours, and has a half-life of 8 to 15 hours. Approximately 25% is excreted renally and the rest through hepatic metabolism and the intestines. The only potential drug–drug interactions reported are with potent CYP3A4 inhibitors. Apixaban is currently being evaluated in 2 Phase III trials. The Apixaban for Reduction In S'Troke and Other ThromboemboLic Events in atrial fibrillation (ARISTOTLE) trial is comparing apixaban at 5 mg twice a day with dose-adjusted warfarin, and the Apixaban VERsus acetylsalicylic acid (ASA) to pRevent strokes [AVERROES] trial is comparing apixaban at 2.5 or 5 mg twice a day with aspirin at 81 to 324 mg daily for the prevention of stroke and systemic embolism in patients with atrial fibrillation.

Edoxaban has 45% to 50% bioavailability, reaches peak plasma concentration in 1 to 2 hours, and has a half-life of 9 to 11 hours. It is predominantly renally excreted. Edoxaban is being evaluated in the Phase III Effective AntiXa Generation in Atrial Fibrillation (ENGAGE AF TIMI) 48 trial at 30 and 60 mg daily versus dose-adjusted warfarin for stroke prevention in patients with atrial fibrillation.

Rivaroxaban has 60% to 80% relative bioavailability, reaches peak plasma concentrations in 2 to 4 hours, and has a half-life of 9 to 13 hours. It is 66% renally excreted. Rivaroxaban at 20 mg daily is being compared with dose-adjusted warfarin for stroke prevention in the Phase III Rivaroxaban—Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonist for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial.

Betrixaban has 34% to 47% absolute bioavailability, a half-life of 15 to 20 hours, and minimal renal excretion. It recently completed Phase II evaluation for stroke prevention in patients with atrial fibrillation in the EXPLORE Xa trial. Betrixaban is being codeveloped with an antidote and there are no or very little drug interactions expected. It is likely to enter Phase III evaluation in the future.

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