

# Emerging options to prevent stroke in atrial fibrillation patients

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**Abstract:** Atrial fibrillation is a common condition in the population and increases in prevalence with age. A new method for evaluating stroke risk with atrial fibrillation, called CHA<sub>2</sub>DS<sub>2</sub>-Vasc, has been developed, as has a novel method for estimating the risk of bleeding, called HAS-BLED. Further, the last decade has seen a dramatic increase in the number of treatment options tested for this condition. These include novel oral anticoagulants such as apixaban, dabigatran, and rivaroxaban, and devices that occlude the left atrial appendage, such as WATCHMAN. This review will compare these new agents with the historical gold standard of warfarin.

**Keywords:** stroke, atrial fibrillation, treatment

## Introduction to the management issues for atrial fibrillation

Precise knowledge of the risk of developing atrial fibrillation across the lifespan and the risk of stroke related to the condition dates back to the 1980s when data from the Framingham Heart Study emerged.<sup>1</sup> In the 1990s, warfarin was a clearly superior treatment option for reduction of stroke risk.<sup>2</sup> In the 2000s, alternative treatment options, including novel anticoagulants, antiplatelet agents, and devices, were explored. Considered in a broad perspective, a tremendous amount of progress has been made in understanding the epidemiology of this disease and its treatment.

This article will review the epidemiology of atrial fibrillation and treatment options. Many emerging treatment options will expand the choices for treatment to at least five choices. It is likely that there will be even more choices in the future.

## Prevention of stroke in atrial fibrillation patients: an overview

Atrial fibrillation affects approximately 0.4% of the population. The prevalence dramatically increases with age. In the Framingham Heart Study, approximately 2% of people aged 60 years were affected, with the number doubling each decade such that 8% of octogenarians had atrial fibrillation.<sup>3</sup>

The risk of stroke is similarly correlated with age.<sup>3</sup> Among those aged 50–59 years, the risk is approximately 1.5% per year. For those aged 80–89 years, the risk is 23% per year.

The scoring system most widely accepted for risk assessment in atrial fibrillation is CHADS<sub>2</sub>. The individual components are as follows: Congestive heart failure, Hypertension, Age  $\geq$  75 years, Diabetes, and previous Stroke or transient ischemic attack (TIA).

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**Table 1** CHADS<sub>2</sub> scoring system

Item	Score (if present)
Congestive heart failure	1
Hypertension	1
Age ≥75 years	1
Diabetes	1
Previous stroke or transient ischemic attack	2

The scoring method is shown in Table 1. The minimum score is 0 and the maximum score is 6. The greater the score, the greater is the risk of subsequent stroke. A score of 2 or greater is generally accepted as an indication for anticoagulation, whereas a score of 0 indicates that the risk of stroke is so low that there is no net benefit to anticoagulation. A score of 1 is more difficult to assess because some patients have a low risk while others have risks approaching those with a score of 2.

As a result of this challenge in deciding which patients with a score of 1 should receive treatment, the CHA<sub>2</sub>DS<sub>2</sub>VASc score was created.<sup>4</sup> The scoring is modeled on CHADS<sub>2</sub>, but additional items are added as follows: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, previous Stroke or TIA, Vascular disease (eg, coronary artery disease), Age 65–74 years, and female Sex Category. The scoring method is shown in Table 2. The minimum score is 0 and the maximum score is 9. Using this classification scheme, patients with a score of 1 carry a much lower risk of stroke than patients with a score of 1 with CHADS<sub>2</sub> and can more safely be assigned to no treatment (Table 3).

HAS-BLED is a novel scoring system used to assess the risk of bleeding in patients with atrial fibrillation being considered for antithrombotic medication.<sup>5,6</sup> The scoring system comprises nine items as follows: Hypertension (>160 mmHg), Abnormal renal/liver function (1 point for creatinine >2.6 mg/dL; 1 point for cirrhosis or bilirubin more than twice normal or aspartate aminotransferase/alanine

**Table 2** CHA<sub>2</sub>DS<sub>2</sub>VASc scoring system<sup>4</sup>

Item	Score (if present)
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes	1
Previous stroke or transient ischemic attack	2
Vascular disease	1
Age 65–74 years	1
Female sex category	1

**Note:** Data from Olesen et al.<sup>4</sup>

**Table 3** Stroke risk with atrial fibrillation according to CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scoring systems<sup>4</sup>

Category	1 year <sup>a</sup>	5 years <sup>a</sup>	10 years <sup>a</sup>
CHADS <sub>2</sub> = 0	1.67	1.28	1.24
CHADS <sub>2</sub> = 1	4.75	3.70	3.56
CHADS <sub>2</sub> = 2–6	12.27	8.30	7.97
CHA <sub>2</sub> DS <sub>2</sub> VASc = 0	0.78	0.69	0.66
CHA <sub>2</sub> DS <sub>2</sub> VASc = 1	2.01	1.51	1.45
CHA <sub>2</sub> DS <sub>2</sub> VASc = 2–9	8.82	6.01	5.72

**Note:** <sup>a</sup>Admission and death due to thromboembolism (peripheral artery embolism, ischemic stroke, and pulmonary embolism) per 100 person-years. Reproduced from Olesen JB, Lip GY, Hansen MK, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124 with permission of the publisher.

aminotransferase/alkaline phosphatase more than three times normal), Stroke history, prior major Bleeding history or predisposition to bleeding, Labile international normalized ratio (INR), Elderly (>65 years), Drugs/alcohol (1 point for antiplatelet agents or nonsteroidal anti-inflammatory drugs, 1 point for alcohol usage history). The risk of bleeding increases with higher scores. For example, a score of 1 point indicates a risk of 1.02 bleeds per 100 patient-years, whereas a score of 5 points indicates a risk of 12.50 bleeds per 100 patient-years.

## Overview of current therapeutics strategies used in atrial fibrillation and stroke, antithrombotics, and antiarrhythmics

The standard by which all treatments are measured for the treatment of atrial fibrillation is warfarin. First synthesized in 1940,<sup>7</sup> the drug has been used in a wide variety of indications, including venous thromboembolism. However, its efficacy in atrial fibrillation has been proven beyond any doubt. Despite its substantial efficacy in atrial fibrillation, an interest in alternative anticoagulants emerged primarily because of concerns regarding the rates of intracranial hemorrhage, the challenges of maintaining a therapeutic range of anticoagulation, and blood monitoring requirements.

As a result, a number of agents have been studied, which has led to an increase in the range of treatment options over the last decade. The main categories of anticoagulants researched include direct thrombin inhibitors (including ximelagatran and dabigatran) and factor Xa inhibitors (including rivaroxaban and apixaban). Because clopidogrel has modest efficacy in generalized atherothrombotic conditions, it was also investigated as a potential alternative to warfarin.

The details of the studies investigating the efficacy and safety of newer agents are described in detail in the next section.

## Advantages, disadvantages, and comparison of different therapeutic approaches

### Antithrombotics

#### Ximelagatran

Ximelagatran is of interest for historical reasons. It was the first oral anticoagulant to be compared with warfarin for the prevention of stroke in atrial fibrillation. In the Stroke Prevention with the Oral Direct Thrombin Inhibitor Ximelagatran compared with Warfarin in Patients with Non-valvular Atrial Fibrillation (SPORTIF) III trial, the rates of stroke or systemic embolism were 1.6% per year with ximelagatran and 2.3% per year with warfarin.<sup>8</sup> In SPORTIF V, the rates of stroke or systemic embolism were 1.6% per year with ximelagatran and 1.2% per year with warfarin.<sup>9</sup> The rates of major bleeding were similar. Ultimately, the US Food and Drug Administration (FDA) chose not to approve ximelagatran, on the basis of three cases of fatal liver disease.

#### Warfarin, aspirin, or neither

A meta-analysis of 29 randomized trials including 28,044 patients found an advantage of warfarin and aspirin over treatment without antithrombotics.<sup>2</sup> Specifically, in the six warfarin versus control studies, which included 2900 patients, warfarin reduced the risk of stroke by 64%. In the eight trials of antiplatelets versus control, which included 4876 patients, the risk of stroke was reduced by 22%. In the 12 head-to-head trials of warfarin and antiplatelets including 12,963 patients, warfarin reduced the risk of stroke by 39%. The absolute increases in the risk of bleeding ( $\leq 3\%$  per year) were less than the absolute risks of stroke without anticoagulation (over 10% per year in stroke patients). A 1-month supply of warfarin is approximately US\$14. A 1-month supply of aspirin is approximately less than US\$1.

#### Warfarin plus aspirin

Low-intensity fixed-dose warfarin (INR 1.2–1.5) plus aspirin 325 mg daily has been compared with adjusted-dose warfarin (INR 2–3) in the Stroke Prevention in Atrial Fibrillation III trial.<sup>10</sup> The trial was stopped after a mean follow-up of 1.1 years because of an increased risk of stroke and systemic embolism with low-dose warfarin and aspirin (7.9% per year) than with adjusted-dose warfarin (1.9% per year). The rates of major bleeding were similar in both groups. At this time

there have been no trials comparing adjusted-dose warfarin alone versus adjusted-dose warfarin plus aspirin in patients with atrial fibrillation.

#### Aspirin plus clopidogrel

The notion that dual antiplatelet agents might be superior to warfarin was tested in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) trial. Clopidogrel 75 mg plus aspirin 75–100 mg once daily was compared with warfarin (target INR 2–3).<sup>11</sup> Patients with atrial fibrillation and one other risk factor were randomized. The primary outcome measure was first occurrence of stroke, noncentral nervous systemic embolus, myocardial infarction, or vascular death. A total of 6706 patients were enrolled, including 1020 with prior stroke or TIA. Mean age was 70 years and 67% of patients were male. Median follow-up was 1.3 years and the mean CHADS<sub>2</sub> score was 2.0. Patients taking warfarin were on target 63.8% of the time. At 18 months, 13.8% of the aspirin/clopidogrel group had discontinued treatment, compared with 7.8% of warfarin patients. The study was stopped early because of a significant advantage of warfarin. The primary outcome measure occurred at a rate of 5.60% per year in the aspirin/clopidogrel group and 3.93% per year in the warfarin group. Ischemic stroke occurred at a rate of 2.15% per year in the aspirin/clopidogrel patients and 1.0% per year in the warfarin patients. Hemorrhagic stroke occurred at a rate of 0.12% per year in the aspirin/clopidogrel group and 0.36% per year in the warfarin group. Major bleeding occurred at a rate of 2.42% per year in the aspirin/clopidogrel group and 2.21% per year in the warfarin group.

ACTIVE was designed to test the hypothesis that the combination of aspirin and clopidogrel was superior to aspirin alone in patients with atrial fibrillation who were deemed unsuitable for warfarin. Clopidogrel 75 mg daily plus aspirin 75–100 mg daily was compared with aspirin 75–100 mg daily plus placebo.<sup>12</sup> Patients with atrial fibrillation at increased risk for stroke in whom warfarin was deemed unsuitable were randomized. A total of 48.9% of patients deemed unsuitable were those who declined to take warfarin. The primary outcome measure was stroke, systemic embolism, myocardial infarction, or death. A total of 7554 patients were enrolled, including 992 with prior stroke or TIA. The average age was 71 years and 58% of patients were male. Median follow-up was 3.6 years and mean CHADS<sub>2</sub> was 2.0. The rate of medication discontinuation at 4 years was 39.4% with clopidogrel and 37.1% with placebo. The primary outcome measure occurred at a rate of 6.8%

per year in the aspirin/clopidogrel group and 7.6% per year in the aspirin/placebo group. Ischemic strokes occurred at a rate of 1.9% per year in the aspirin/clopidogrel group and 2.8% per year in the aspirin/placebo group. Hemorrhagic stroke occurred at a rate of 0.2% per year in both groups. The rates of myocardial infarction were similar in both groups (<1% per year). Major bleeding occurred at a rate of 2.0% per year in the aspirin/clopidogrel group and 1.3% per year in the aspirin/placebo group. The major site of bleeding was gastrointestinal. The risk of intracranial hemorrhage doubled from 0.2% per year to 0.4% per year with the aspirin/clopidogrel combination. A 1-month supply of clopidogrel is approximately US\$200.

### Dabigatran

In the Randomized Evaluation of Long-term Anticoagulant Therapy study, dabigatran 110 mg twice daily or 150 mg twice daily were compared with warfarin (target INR 2.0–3.0).<sup>13</sup> Patients with atrial fibrillation at increased risk for stroke were randomized to one of the three treatments. The primary outcome measure was stroke or systemic embolism. A total of 18,113 patients were enrolled, including 3623 with prior stroke or TIA. Average age was 71.8 years and approximately 63% of patients were male. Median follow-up was 2.0 years and the mean CHADS<sub>2</sub> score was 2.1. Approximately one-third of patients each had a CHADS<sub>2</sub> score of 0–1, 2, and 3–6. The median time spent in a therapeutic INR for warfarin patients was 64%. The rates of medication discontinuation were 20.7% for dabigatran 110 mg, 21.2% for dabigatran 150 mg, and 16.6% for warfarin. The primary outcome measure occurred at a rate of 1.53% per year in the dabigatran 110 mg group, 1.11% per year in the dabigatran 150 mg group, and 1.69% per year in the warfarin group. There was no significant difference in the rate of ischemic stroke, but hemorrhagic stroke occurred significantly less frequently with dabigatran than with warfarin (0.12% per year in the dabigatran 110 mg group, 0.10% in the dabigatran 150 mg group, and 0.38% per year in the warfarin group). Myocardial infarction occurred at an increased rate with dabigatran: 0.72% per year with 110 mg ( $P = 0.07$  compared with warfarin), 0.74% per year with 150 mg ( $P = 0.048$  compared with warfarin), and 0.53% per year with warfarin. The rate of major bleeding was 2.71% per year in the dabigatran 110 mg group, 3.11% per year in the dabigatran 150 mg group, and 3.36% per year in the warfarin group. Gastrointestinal hemorrhage was significantly higher with dabigatran 150 mg compared with warfarin (1.51% per year versus 1.02% per year). Mortality was less in the dabigatran patients (3.75%

per year in the 110 mg group, 3.64% per year in the 150 mg group, and 4.13% per year in the warfarin group). There was no change in liver enzymes.

The FDA chose not to approve the 110 mg dose because it could not identify any subgroup in which the 100 mg group did not represent a substantial disadvantage compared with the 150 mg group.<sup>14</sup> A 75 mg dose is available for patients with chronic kidney disease. The 110 mg doses are approved for use in Canada and Europe.

Postmarketing reports indicate occurrences of gastrointestinal hemorrhages in patients aged 80 years or older, including a fatal event.<sup>15</sup> The authors suggest that older patients are more frequently affected by chronic kidney disease, have lower body weight, and are taking additional medications that may interact with dabigatran. They suggest caution using dabigatran in these patients. A 1-month supply of dabigatran is currently approximately US\$250.

### Apixaban

The Apixaban Versus Acetylsalicylic Acid to Prevent Strokes randomized trial compared apixaban 5 mg twice daily with aspirin 81–324 mg daily in patients with atrial fibrillation at increased risk for stroke for whom warfarin was deemed unsuitable.<sup>16</sup> Examples of unsuitable patients for warfarin cited in the study were those who had difficulty maintaining a therapeutic INR, patients at moderate risk only, and patients who refused warfarin; the latter group comprised 37% of patients. More than half of patients had multiple reasons for being considered unsuitable for warfarin. A total of 5599 patients were enrolled, including 764 with prior stroke or TIA. Mean age of patients was 70 years and 59% were male. A total of 34% of patients were aged 75 or older. Median follow-up was 1.1 years and mean CHADS<sub>2</sub> score was 2.0. Approximately one-third of patients each had a CHADS<sub>2</sub> score of 0–1, 2, and 3–6. The rates of medication discontinuation were 17.9% per year with apixaban and 20.5% per year with aspirin. The primary outcome measure occurred at a rate of 1.6% per year in the apixaban group and 3.7% per year in the aspirin group. Ischemic stroke occurred at a rate of 1.1% per year with apixaban and 3.0% per year with aspirin. Hemorrhagic stroke occurred at a rate of 0.2% per year with apixaban and 0.3% per year with aspirin. Myocardial infarction occurred at a rate of 0.8% per year with apixaban and 0.9% per year with aspirin. Major bleeding occurred at a rate of 1.4% per year with apixaban and 1.2% per year with warfarin. The rates of gastrointestinal hemorrhage were also similar (approximately 1% per year). Mortality was

3.5% per year in the apixaban group and 4.4% per year in the aspirin group.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial, apixaban 5 mg twice daily was compared with warfarin (target INR 2.0–3.0) in patients with atrial fibrillation and one other risk factor.<sup>17</sup> The primary outcome measure was stroke or systemic embolism. A total of 18,201 patients were enrolled, including 3436 with prior stroke or TIA. Median age was 70 years and 65% of patients were male. A total of 31% of patients were aged 75 or older. Median follow-up was 1.8 years and mean CHADS<sub>2</sub> score was 2.1. Approximately one-third of patients each had a CHADS<sub>2</sub> score of 1, 2, and 3–6. The median time spent in a therapeutic INR for warfarin patients was 66%. The rates of medication discontinuation were 25.3% with apixaban and 27.5% with warfarin. The primary outcome measure occurred at a rate of 1.27% per year in the apixaban group and 1.60% per year in the warfarin group. Ischemic stroke occurred at a rate of 0.97% per year with apixaban and 1.05% per year with warfarin. Hemorrhagic stroke occurred at a rate of 0.24% per year with apixaban and 0.47% per year with warfarin. Myocardial infarction occurred at a rate of 0.53% per year with apixaban and 0.61% per year with warfarin. Major bleeding occurred at a rate of 2.13% per year with apixaban and 3.09% per year with warfarin. Rates of gastrointestinal hemorrhage were similar. The FDA is currently reviewing apixaban. If approved, a 1-month supply of apixaban is expected to be approximately US\$250.

### Rivaroxaban

Rivaroxaban 10 mg once daily was compared with warfarin (target INR 2–3) in Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.<sup>18</sup> Patients with atrial fibrillation at increased risk for stroke were randomized. The primary outcome measure was stroke or systemic embolism. Importantly, the primary outcome was based on efficacy analysis rather than intention to treat. All other medication trials used the intention-to-treat analysis as the basis for comparison. A total of 14,264 patients were enrolled, including 7811 with prior stroke or TIA. Median age was 73 years and 60% of patients were male. A quarter of patients were 78 years or older. Median follow-up was 1.9 years and the mean CHADS<sub>2</sub> score was 3.5, which represents a significantly higher-risk group than in other studies. A total of 13% of patients had a CHADS<sub>2</sub> score of 2 and the other 87% had a score of 3–6. The median time spent in a therapeutic INR

for warfarin patients was 58%, which was significantly worse than in other trials. The rates of medication discontinuation were 23.7% with rivaroxaban and 22.2% with warfarin. In the intention-to-treat analysis (how other trials are reported), the primary outcome measure occurred at a rate of 2.1% per year in the rivaroxaban group and 2.4% per year in the warfarin group. In the per protocol analysis, the primary outcome measure occurred at a rate of 1.7% in the rivaroxaban group and 2.2% per year in the warfarin group. In the per protocol population, ischemic stroke occurred at a rate of 1.34% per year with rivaroxaban and 1.42% per year with warfarin. Hemorrhagic stroke occurred at a rate of 0.26% per year with rivaroxaban and 0.44% per year with warfarin. Myocardial infarction occurred at a rate of 0.91% per year with apixaban and 1.12% per year with warfarin. Major bleeding occurred at a rate of 3.6% per year in the rivaroxaban group and 3.4% per year in the warfarin group. Gastrointestinal hemorrhage was more common with rivaroxaban. The FDA approved rivaroxaban in 2011. The cost is expected to be approximately US\$250 for a 1-month supply.

### Antiarrhythmics

To date, no randomized trials have definitively shown a benefit of rhythm control versus rate control in atrial fibrillation.<sup>19–23</sup> Specifically, stroke rate is not reduced with assignment to rhythm control in these trials. Clinically silent recurrences of atrial fibrillation may occur in asymptomatic patients treated with antiarrhythmic drugs and lead to stroke. In Atrial Fibrillation Follow-up Investigation of Rhythm Management, the majority of strokes occurred after warfarin had been stopped or when the INR was subtherapeutic.<sup>20</sup> Consequently, the most recent guidelines from the American College of Cardiology Federation, American Heart Association, Heart Rhythm Society, and European Society of Cardiology state that anticoagulation may be required in high-risk patients regardless of antiarrhythmic use.<sup>24</sup> A post hoc analysis of the Placebo-controlled, Double-blind, Parallel-arm Trial to Assess the Efficacy of Dronedronone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from any cause in Patients With Atrial Fibrillation/Atrial Flutter found a reduction in the risk of stroke from 1.8% per year to 1.2% per year in patients who received dronedronone in addition to antithrombotic therapy and heart rate control.<sup>25</sup> This hypothesis-generating finding may form the basis for a future trial with dronedronone in patients with atrial fibrillation in which stroke will be a primary endpoint.

## Devices

### WATCHMAN device

In the Embolic Protection in Patients with Atrial Fibrillation trial, percutaneous closure of the left atrial appendage with the WATCHMAN® device (Atritech, Inc, Plymouth, MN) was compared with warfarin (target INR 2–3).<sup>26</sup> Patients with atrial fibrillation and one other risk factor were randomized in a 2:1 fashion (two patients to the WATCHMAN device to one patient with warfarin). The primary outcome measure was stroke, death, or systemic embolism. A total of 707 patients were enrolled, including 131 with a prior stroke or TIA. The mean age was approximately 72 years and 70% of patients were male. A greater percentage of patients were 75 years or older in the warfarin group (47.1%) than the device group (41.0%). Mean follow-up was 18 months and mean CHADS<sub>2</sub> score was 2.2. Patients in the warfarin group were in target 66% of the time. The device was successfully implanted in 88% of patients. The primary outcome measure occurred at a rate of 3.0% per year in the device group and 4.9% per year in the warfarin group. Ischemic stroke occurred at a rate of 2.2% per year in the device group and 1.6% per year in the warfarin group. Hemorrhagic stroke occurred at a rate of 0.1% per year in the device group and 1.6% per year in the warfarin group. The rate of hemorrhagic stroke with warfarin is much higher than previous studies. Serious adverse events, including major bleeding, pericardial effusion, and device embolization, occurred at a rate of 7.4% per year in the device group and 4.4% per year in the warfarin group. The cost of the WATCHMAN device is approximately US\$10,000 and procedural costs are approximately US\$20,000. The WATCHMAN device has not been compared with newer anticoagulants.

Table 4 summarizes the list of currently or soon to be available medical treatment options for the prevention of stroke in patients with atrial fibrillation. Direct comparisons between agents, which have not been compared within the same clinical trial, should be made with caution because of potential differences in study populations.

### Guideline recommendations

The American College of Cardiology, American Heart Association, and Heart Rhythm Society released a focused update on the management of patients with atrial fibrillation in 2011.<sup>24</sup> The new guidelines recommend:

- Against targeting a heart rate of less than 80 during rest or less than 100 during a 6-minute walk in patients with atrial fibrillation who have an ejection fraction greater than 40% and are without symptoms<sup>27</sup>
- Consideration of aspirin and clopidogrel in patients deemed unsuitable for anticoagulation with warfarin<sup>12</sup>
- Consideration of dronedarone in patients with paroxysmal atrial fibrillation in order to decrease the need for hospitalization<sup>28</sup>
- Avoidance of dronedarone in patients with atrial fibrillation and class IV heart failure or those with decompensated heart failure in the previous 4 weeks.<sup>29</sup>

Recommendations regarding the newer antithrombotics (ie, dabigatran, rivaroxaban, and apixaban) and the WATCHMAN device were not included in the guidelines because they had not been approved at the time of guideline writing. The committee indicated that changes would be forthcoming in the near future.

### Optimizing patient management programs

One of the challenges in managing patients with warfarin has been regulation of the patient's INR. There are a number of methods for regulation of INR, including a physician's office practice, an anticoagulation clinic, and home self-monitoring. The 2002 Managing Anticoagulation Services Trial did not find an advantage of anticoagulation services over usual care in respect of time spent in the target range for INR (55.6% versus 52.3%).<sup>30</sup> These results are worse than those seen in more recent trials of anticoagulation for atrial fibrillation where time spent in target is at least 60%.<sup>13,17,26</sup> A 2006 systematic review of 67 studies including 50,208 patients found that patients were in the therapeutic window approximately 63.6% of the time. Patients managed in community practices had significantly less control than patients managed in an anticoagulation clinic. Those who self-managed their INR had the best rate of therapeutic control. The rates in target were 56.7% in a community practice, 65.6% in an anticoagulation clinic, and 71.5% with self-management.<sup>31</sup> Another systematic review and meta-analysis found that self-management improves the overall outcomes with oral anticoagulation.<sup>32</sup> Self-monitoring reduced thromboembolic events by 55%, mortality by 31%, and major hemorrhage by 35%. A more recent meta-analysis of home self-monitoring and self-adjustment versus usual care found a 26% lower risk of death, a 42% lower risk of major thromboembolism, and an 11% reduction in major bleeding.<sup>33</sup> Patient satisfaction and quality of life were improved with self-monitoring and self-adjustment compared with usual care. Somewhat contrary to these findings, THINRS (The Home INR Study) found that among 2922 randomly assigned subjects with atrial fibrillation or mechanical heart valves followed for a

**Table 4** Treatment options for stroke prevention in atrial fibrillation

Medication name	Clinical trial	Comparator	Mean CHADS <sub>2</sub> score	Strokes per year (%)	ICH per year (%)	Major bleeding per year (%)
Apixaban	AVERROES <sup>16</sup>	Aspirin	2.0	1.6	0.2	1.4
Apixaban	ARISTOTLE <sup>17</sup>	Warfarin	2.1	1.19	0.24	2.13
Aspirin	Meta-analysis <sup>2</sup>	Control	NA	3.2	NA	NA
Aspirin plus clopidogrel	ACTIVE <sup>12</sup>	Aspirin	2.0	2.4	0.4	2.0
Aspirin plus clopidogrel	ACTIVE W <sup>11</sup>	Warfarin	2.0	2.39	0.12	2.42
Dabigatran 150 mg	Re-LY <sup>13</sup>	Warfarin	2.1	1.01	0.10	3.11
Rivaroxaban	ROCKET-AF <sup>18</sup>	Warfarin	3.5	1.65	0.26	3.6
Warfarin	Meta-analysis <sup>2</sup>	Control	NA	1.4	NA	NA
Warfarin	Meta-analysis <sup>2</sup>	Aspirin	NA	NA	NA	NA
WATCHMAN	PROTECT-AF <sup>26</sup>	Warfarin	2.2	2.3	0.1	3.5

**Abbreviations:** ACTIVE W, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Strokes; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ICH, intracranial hemorrhage; PROTECT-AF, Embolic Protection in Patients with Atrial Fibrillation; Re-LY, Randomized Evaluation of Long-term Anticoagulant Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; NA, not available.

minimum of 2 years, the rate of stroke, major bleeding, or death was not significantly reduced among those with weekly self-testing versus those monitored in a high-quality testing clinic.<sup>34</sup> The self-testing group spent 3.8% more time in target (66.2% versus 62.4%) and expressed greater satisfaction with anticoagulation therapy and quality of life.

Patient preference is an extremely important variable in decision making regarding anticoagulation in atrial fibrillation. In both the ACTIVE W<sup>11</sup> and Apixaban Versus Acetylsalicylic Acid to Prevent Strokes<sup>16</sup> trials, at least a third of patients were deemed unsuitable for treatment because the patient declined oral anticoagulation with warfarin. In studies of shared decision making, fewer patients opt for oral anticoagulation than what is suggested in published guidelines.<sup>35</sup> A decision aid has been developed for patients with atrial fibrillation, but a formal study evaluating its efficacy has not been performed.<sup>36</sup> The decision guide would need updating in light of the many new agents that are currently available.

## Conclusion and future directions

Atrial fibrillation is a common condition in the population and increases with age. Risk stratification schemes help best define who is most likely to suffer from stroke. Given the aging population, the issue of treating atrial fibrillation will become even more relevant.

The range of options for the treatment of atrial fibrillation has expanded in the last decade. Good treatment options include apixaban, dabigatran, rivaroxaban, and warfarin. Left atrial appendage closure is a consideration for patients who have difficulty with medication compliance, but the immediate procedural risks must be weighed against the potential benefit. Because of cost issues, warfarin is likely

to be first-line treatment for many patients in the near future. Second-line treatments for atrial fibrillation include aspirin and clopidogrel in combination and aspirin alone. Given the superiority of apixaban over aspirin, it is difficult to define a scenario where aspirin and clopidogrel would be a good second option.

Self-management of anticoagulation yields the best results if it can be performed successfully. Alternative management strategies include anticoagulation clinics and office-based management, with the former being more successful than the latter.

Future directions include the development of reversal agents for patients who develop intracranial hemorrhage while taking a direct thrombin or factor Xa inhibitor. Already, an animal study suggests that agents for such purpose may already be available.<sup>37</sup> The agent found to be most useful was prothrombin complex concentrate (PCC) at a dose of 100 U/kg mouse weight. PCC effectively prevented the hematoma expansion induced by dabigatran. The hematoma expansion associated with dabigatran occurred primarily in the first 3 hours, consistent with previous studies of hematoma expansion following intracerebral hemorrhage. Specifically, 77% of the maximum volume was reached within the first hour and 86.7% within 3 hours. The implication is that, if ultimately proven effective, PCC will have to be given within 3 hours of the incident bleeding. In a separate human volunteer study including 12 healthy males, PCC 50 IU/kg completely reversed the anticoagulant effects of rivaroxaban (ie, prothrombin time), whereas PCC at the dose tested in this study had no effect on the anticoagulant activity of dabigatran (ie, activated partial thromboplastin time, ecarin clotting time, and thrombin time).<sup>38</sup> At this time, additional studies will be needed to determine the utility of PCC for

reversal of intracerebral hemorrhage associated with oral anticoagulation.

Additional directions include new devices with less immediate periprocedural risk. One other device has been tested but no longer appears to be in development by the manufacturer. The device, called PLAATO (percutaneous left atrial appendage transcatheter occlusion; Appriva Medical, Inc, Sunnyvale, CA), was associated with an immediate serious adverse event rate of 3.6%, including one patient who died and three patients who experienced hemopericardium.<sup>39</sup> During an average follow-up of 9.8 months, 1.8% of patients experienced stroke (approximately 2.2% per year). For now, oral treatment of atrial fibrillation is the preferred method but may change if devices improve.<sup>40</sup>

## Disclosure

Dr Silver has served as a defense expert in medical malpractice cases of stroke and has received compensation for work done for Medscape, MedLink, and Oakstone Publishing.

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