Drug Therapies for Stroke Prevention in Atrial Fibrillation
An Historical Perspective

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KEYWORDS

• Stroke prevention • Atrial fibrillation • Oral anticoagulants

KEY POINTS

In patients with atrial fibrillation:

- Increasing age is a major stroke risk, but the elderly, who need stroke prophylaxis therapy the most, are less likely to receive anticoagulant therapy.
- Aspirin is of questionable use for stroke prophylaxis.
- The new oral anticoagulants are largely an upgrade from warfarin therapy for stroke prophylaxis, but well managed warfarin therapy remains an acceptable and inexpensive treatment option.

INTRODUCTION

In a letter to *The Lancet* on June 10, 1972,[1] C. Miller Fisher, a neurologist at the Massachusetts General Hospital in Boston, wrote the following:

> *Sir, Your editorial (May 6, p. 1002) on the electrical conversion of atrial fibrillation provides an opportunity to comment on the long-term management of the many patients who remain in fibrillation. In our cerebrovascular studies, we have been struck by the number of patients in atrial fibrillation who have a severe stroke as the first manifestation of embolism. In the past year, 11 such patients, all over the age of 60, have been admitted to the Massachusetts General Hospital, and of these, 8 had otherwise been in relatively good health. 7 were diagnosed as having arteriosclerotic heart-disease, 4 rheumatic. It is our impression from this experience that all patients with chronic atrial fibrillation should be considered for longer-term prophylactic anticoagulant therapy before the first embolus. It is, of course, realised that the total number of those in fibrillation from whom these patients were selected is unknown, but this may not be important, since anticoagulant therapy reduces embolism and, when carefully regulated, is safe, particularly when compared with the prospect of a major stroke and a fate almost worse than death itself.*

Thus, not so long ago, not only was the association of atrial fibrillation with stroke not well appreciated, but also neither was the prospect of long-term anticoagulation for stroke prevention. Not so long ago, the association of atrial fibrillation with embolic stroke, and the possibility of its prevention with oral anticoagulation, was only an idea. It was even believed that atrial fibrillation was only a marker for stroke, rather than a cause. It took a study from Framingham[2] to put that notion to rest. The Framingham group compared the incidence of strokes in patients in their 60s, 70s, and 80s who did not have atrial fibrillation with those who did. As expected, the incidence of stroke in patients without atrial fibrillation increased with each decade, but in each decade,

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there were always about 5 times more strokes in people with than without atrial fibrillation (Table 1). That study made it clear that atrial fibrillation was not simply a marker, but rather a cause of embolic stroke. However, it has also been known for many years that not all strokes in patients with atrial fibrillation are caused by clots that embolize from the left atrium.[3]

The Establishment of Warfarin Therapy for Stroke Prevention in Atrial Fibrillation

This review most often refers to warfarin rather than vitamin K antagonists (VKAs). That decision is because many of the studies cited used warfarin rather than other VKAs. In some studies, the type of VKA used was optional, but data on warfarin are applicable to all VKAs.

The efficacy of warfarin for stroke prevention in atrial fibrillation was shown by 5 intention-to-treat trials performed in the late 1980s and into the 1990s. They were the AFASAK (Copenhagen Atrial Fibrillation, Aspirin, Anti-Koagulation) trial,[4] the SPAF I (Stroke Prevention in Atrial Fibrillation I) trial,[5] the BAATAF (Boston Area Anticoagulation Trial for Atrial Fibrillation) trial,[6] the CAFA (Canadian Atrial Fibrillation Anticoagulation) trial,[7] and the SPINAF (Stroke Prevention in Nonvalvular Atrial Fibrillation) trial.[8] They were all prospective, randomized, placebo-controlled trials of warfarin versus placebo for the prevention of thromboembolic complications associated with atrial fibrillation. Some of these studies included randomization to an aspirin arm. All reported significant efficacy of warfarin over placebo except CAFA.[7] That study was stopped early before completion of its planned recruitment of 630 patients because of the publication of 2 other positive studies of similar design and objective. Thus, although the study showed efficacy for warfarin compared with placebo (Fig. 1), the confidence intervals (CIs) were wide because the study randomized only 187 patients to warfarin and 191 patients to placebo. Nevertheless, when the data were pooled from these 5 studies,[9] they showed a risk reduction of 68% (P = .001; 95% CI, 50–79). When an on-treatment analysis of these studies was performed, there was an 83% risk reduction (P<.001; 95% CI, 69–90).[10] This factor essentially means that if warfarin is given to a patient with atrial fibrillation and an international normalized ratio (INR) in the therapeutic range (2–3) is maintained, the patient's risk for stroke is reduced to the same level as the risk that would be present if they were in sinus rhythm.

Most of those studies were performed in an era before the INR became a standard for measuring the adequacy of anticoagulation when using a VKA. Use of the INR was an important milestone, especially because a therapeutic range, with a target INR of 2.5, was established.[11,12] It also became clear that when the INR decreased to less than 2, there was a steep increase in the odds ratio for stroke, such that an INR of 1.7 doubled the risk of stroke, and an INR of 1.5 more than tripled the risk of stroke (Fig. 2). Moreover, these studies also showed that the risk of bleeding was flat from an INR of 1.5 to an INR of about 3.5 (Fig. 2). Thus, decreasing the INR to less than 2 does not decrease the risk of bleeding, but does increase the risk of stroke. The lessons learned were that it was important to maintain an INR in the therapeutic range to minimize the occurrence of embolic strokes, and that there was a critical and relatively safe range for this. The reason the target was 2.5 (ie, in the middle of the range) was that there are many uncertainties associated with administration of warfarin, in considerable part because of its interaction with numerous drugs (>100 were listed in the 2004 *Physicians' Desk Reference*) and foods so that the INR could be expected to vary over time.

Table 1
Data from the atrial fibrillation and stroke Framingham study with a 30-year follow-up

Age Group (y)	Previous Atrial Fibrillation (%)	Stroke per 1000 py_O	Stroke per 1000 py_{AF}	Incidence Density Ratio	Pop. AR (%)[a]
60–69	1.8	4.5	21.2	4.7	7.3
70–79	4.7	9.0	48.9	5.4	16.5
80–89	10.2	14.3	71.4	5.0	30.8

Abbreviations: Pop. AR, population attributable risk; py_{AF}, patient years with atrial fibrillation; py_O, patient years, no atrial fibrillation; (y), years.

[a] Adjusted for blood pressure.

Data from Wolf PA, Abbott RD, Kannell WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med 1987;147:1561–4.