See related article, pages 235–240.

In 1989, the Copenhagen AFASAK study reported results from the first randomized, placebo-controlled trial evaluating adjusted-dose warfarin and aspirin in the prevention of stroke for nonvalvular atrial fibrillation (NVAF). Like the 5 randomized, placebo-controlled trials that came after it, the Copenhagen AFASAK study demonstrated a reduction in embolic events in patients taking warfarin. Today, the weight of evidence from 18 trials comparing warfarin with either placebo or antiplatelet drugs overwhelmingly favors the use of warfarin for stroke prevention in NVAF.

In 20 years since AFASAK and 10 years since the first meta-analysis of trials testing the effect of warfarin on stroke risk, anticoagulation has remained underused and opportunities for preventing fatal and disabling stroke have been frequently missed. In this issue of Stroke, Gladstone and colleagues report a prospective practice audit of 920 patients presenting with ischemic stroke and a history of atrial fibrillation to 12 hospitals in Ontario, Canada. All patients had a high risk of stroke. Approximately 60% of the 597 patients with a first-ever stroke were not receiving warfarin at the time of admission. Of those receiving warfarin, approximately three fourths had a subtherapeutic international normalized ratio (INR) recorded on admission. A further 323 patients with a history of stroke or transient ischemic attack arguably had the most to gain from warfarin. Approximately 79% of these were excluded because warfarin was not on warfarin at the time of admission. Physicians excluded 54% of the screened sample of patients because one treatment was preferred over the other. Importantly, 79% of those using warfarin had subtherapeutic INR levels. These findings are disturbing because all patients included in the audit were judged to be “ideal candidates” for warfarin, living independently without known contraindications to anticoagulation. Gladstone et al highlight the severity of stroke in patients with NVAF. Eighty percent of the patients with a first-ever stroke either died or were disabled at discharge (modified Rankin score of 2 or more).

The opinions in this editorial are not necessarily those of the editors or of the American Heart Association.

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Gladstone et al’s study paints a depressing picture that is replicated elsewhere. Taken together, existing research indicates that the suboptimal uptake of warfarin and subtherapeutic anticoagulation is the norm. The implication is clear. Wider uptake of warfarin would reduce death and disability in people with NVAF. Meanwhile, aging populations have an increasing prevalence of NVAF and a growing burden of preventable stroke.

Gladstone et al recognize wider implementation of warfarin as a major challenge. Three main objections are often raised as barriers to the use of warfarin: that it may not be a safe treatment for elderly patients who are presumed to be at greater risk of a major hemorrhage, that the proven benefits of warfarin derived from trials of highly selected patients may not be realized in routine clinical practice, and that therapeutic control is difficult.

The Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) has now resolved the first 2 objections. BAFTA is one of the largest studies of stroke risk reduction in atrial fibrillation in the elderly. BAFTA randomized patients older than age 75 years (average age, 81.5 years). Patients received adjusted-dose warfarin or 75 mg per day of aspirin. Significantly, patients were recruited by primary care physicians and received usual anticoagulation management. Results confirmed the superiority of warfarin over aspirin and demonstrated equivalent risks of major bleeding, even in those older than 85 years of age. A meta-analysis of previous comparisons between warfarin and aspirin demonstrated a relative risk reduction of 38% (95% CI, 18% to 52%) for all strokes and subdural hematoma in favor of warfarin. In comparison, BAFTA demonstrated a relative risk reduction of 47% (95% CI, 19% to 66%).

Previous studies evaluating warfarin had restrictive selection criteria. In BAFTA, only 6.1% of patients did not meet inclusion criteria. According to the uncertainty principle, physicians excluded 54% of the screened sample of patients because one treatment was preferred over the other. Importantly, 79% of these were excluded because warfarin was selected as the drug of choice by the treating physician. BAFTA provides compelling evidence of the effectiveness of warfarin in elderly people. The study demonstrates the safety of warfarin in an elderly cohort and that warfarin’s benefits are generalizable to patients managed in routine clinical practice.

Achieving therapeutic control with warfarin is considered difficult. As a vitamin K antagonist, warfarin has diet and some drug sensitivity. INR levels can be maintained within a therapeutic range approximately 65% to 70% of the time and sub- and supratherapeutic INR levels still confer some protection from stroke. Although better control
would be expected to produce even greater benefit, warfarin is like many cardiovascular prevention measures with benefits realized, although ideal goals or targets are not always achieved.19–21

There has been an immense ongoing effort to find a substitute for warfarin. The “holy grail” is a fixed-dose anticoagulant that safely achieves stable long-term therapeutic control without dose titration and without continual monitoring. Paradoxically, the need for monitoring and variable tailored dosing may be the principal advantage of warfarin over nascent fixed-dose anticoagulants. We give anticoagulants to patients of wide-ranging ages, weights, organ health, and diet who are taking a variety of medications. Early studies of warfarin demonstrated that the risk–benefit tradeoff favored adjusted-dose warfarin over low, fixed-dose warfarin.22

Newer anticoagulants targeting various parts of the coagulation cascade are not immune from problems. Possible limitations of fixed dosing, lack of reversibility at the time of major hemorrhage, and a lack of readily available anticoagulation tests may be barriers to successful use. Safety concerns prompted the withdrawal of the direct thrombin inhibitor, ximelagatran.22 The factor-Xa inhibitor, idraparinux, increased the risk of both intracranial and extracranial hemorrhages when compared with warfarin and the risks were particularly elevated in the elderly in whom benefits need to be realized.23 Trials of dabigatran and rivaroxaban and of other drugs in early stages of development24 may one day signal the demise of warfarin. In the meantime, warfarin is the anticoagulant of choice.

The standard for a next-generation anticoagulant is high. Warfarin is cheap, highly effective in preventing stroke in NVAF, as safe as aspirin, reversible at the time of hemorrhage, readily monitored, and its dosage can be individually tailored. As suggested by Gladstone et al.,5 the priority for researchers and clinicians alike is to more widely implement warfarin in the setting of NVAF. It would be a pity if higher anticoagulation rates in NVAF had to await an international marketing campaign of a new medication.

In outlining potential strategies to bridge the evidence practice gap, Gladstone et al.5 distinguish between system-level and patient/physician-level strategies. A further distinction can be made between approaches that aim to increase the initiation and uptake of warfarin and those that aim to improve ease and quality of warfarin management. Management of INR is relevant to Gladstone et al.’s5 report in which subtherapeutic INRs were commonly found in stroke patients with NVAF. Improved control of warfarin could also improve the uptake and initiation of warfarin. Anticoagulation clinics and patient self-monitoring appear helpful, although not all studies of these interventions have demonstrated improved INR control.15–17 There is certainly scope for further research on improved management of INR on warfarin.

Development of effective strategies for the initiation and uptake of warfarin have proved complex and results have sometimes been counterintuitive. In a randomized study addressing several cardiovascular preventive healthcare activities, a multifaceted intervention was evaluated comprising audit and feedback of practice, academic detailing, and computerized guidelines and reminder systems in a primary healthcare setting. The intensive intervention did not significantly improve anticoagulant prescribing.25 A recently reported randomized evaluation of another multifaceted intervention targeting family physicians also did not improve the management of atrial fibrillation.26 Although patient decision aids improve patient knowledge and reduce decisional conflict, these materials do not appear to influence the uptake of warfarin27 or are only effective in the short-term.28 In a recent evaluation, uptake of warfarin was significantly lower in those receiving a decision aid compared with those receiving evidence-based guidelines in the subgroup of patients not already on warfarin.27

Both physicians and patients have a profound distrust of warfarin. Physicians are less likely to prescribe warfarin for patients with NVAF if an adverse bleeding event on warfarin results in hospitalization of a patient.29 By contrast, physicians do not change their prescribing if a patient with NVAF not on warfarin experiences an ischemic stroke.29 One study has also shown that a significant proportion of patients retract their initial endorsement of an undisclosed treatment for atrial fibrillation on learning it is warfarin.30 It may be that significant work needs to be done to tackle the maligned “brand” image of warfarin.

It must be remembered that individual physicians may have relatively few patients affected by NVAF compared with more prevalent stroke risk factors such as hypertension and diabetes. Confidence in appropriately managing NVAF with warfarin may be comparatively low. Collaborative networks among physicians have been associated with the higher uptake of warfarin among patients with NVAF.11 Building collaborative links between primary care physicians and specialists may prove useful because specialists can offer the reassurance of expert advice and guidance for wary, less experienced physicians caring for patients with NVAF. Gladstone et al.’s5 contribution demonstrates the important role of population-based registries in monitoring evidence-practice gaps and potentially evaluating strategies to improve practice.

Too often and for too long we have overstated the inconvenience of warfarin and exaggerated its risks, ignoring convincing evidence of its effectiveness in practice. Gladstone et al.5 reminds us of the perils of discounting the benefits of warfarin.

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References


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Warfarin: An Inconvenient Truth
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