Controversies Surrounding Long-term Anticoagulation of Very Elderly Patients in Atrial Fibrillation*

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(Abbeviations: AF=atrial fibrillation; INR=international normalized ratio; PT=prothrombin time; SPAF=Stroke Prevention in Atrial Fibrillation study)

Atrial fibrillation (AF) affects more than 2 million people in the United States and is generally managed with lifelong anticoagulation. The median age is approximately 75 years, and one third are >80 years old. As our population ages, the prescription of anticoagulants among very elderly patients will require increasingly close scrutiny and careful reflection1-3 (Table 1).

The benefit of anticoagulation in nonrheumatic chronic AF for prevention of embolic stroke has been demonstrated in numerous studies.4-10 Most of these trials, however, had few patients >75 years of age. How does one apply the results of these trials, with their high compliance rates, excellent monitoring, careful patient selection, and short-term results, to one’s own practice? Specifically, can one realistically apply these results to the very elderly, who are at highest risk for death and disability from AF-related stroke and from intracranial hemorrhage?

Pragmatic and biological issues contribute to the risk of major hemorrhage when the very elderly take warfarin (Table 2). The very elderly are at great risk for falls and may have deficits in auditory and visual acuity. A “tea and toast” diet deficient in vitamin K can potentiate the anticoagulant effect of warfarin.

Elderly patients in whom warfarin is indicated are often receiving numerous other medications, many of which can affect the metabolism of and interact, sometimes unpredictably, with warfarin.

Biological issues include an increased incidence of occult diseases that predispose to hemorrhagic complications of warfarin. One example is amyloid angiopathy, a risk factor for spontaneous intracerebral hemorrhage.11 The incidence of this condition rises with age and likely increases the risk of this dreaded complication of anticoagulation. Older patients are also more likely to have occult GI lesions, such as peptic ulcers, colonic angiodysplasia and diverticuli, and malignancies, all of which increase the risk of major GI bleeding while receiving oral anticoagulants.3

Potential Benefits of Anticoagulation

Six of the seven major randomized trials evaluating antithrombotic therapy in AF4-10 were primary prevention trials of stroke. The seventh, the European Atrial Fibrillation Trial (EAFT), was a secondary prevention trial that compared anticoagulation, aspirin, and placebo in patients with prior stroke or transient ischemic attack. All of these studies, except the second Stroke Prevention in Atrial Fibrillation study (SPAF II),9 showed a reduction in end points for warfarin-treated patients. Analysis of the pooled data from these trials (excluding SPAF II and EAFT) showed a 68% risk reduction for all strokes in patients assigned to anticoagulation.11 The same analysis revealed a 33% reduction in the risk of death in warfarin-treated patients. However, the mean age of participants in these trials was significantly lower than the age distribution of patients with AF in the United States.12

While these results suggest that elderly patients with AF might benefit from warfarin, the only trial to test this hypothesis in a large number of very elderly patients, SPAF II, showed no benefit of warfarin.
over aspirin alone in a group of 385 patients >75 years. In this study, elderly patients assigned to warfarin did have a lower annual rate of ischemic stroke (3.6% per year vs 4.8% in the aspirin-treated group). This benefit, however, was offset by a higher rate of intracranial hemorrhage in the warfarin-treated patients (1.8% per year vs 0.8% in the aspirin-treated group). Although SPAF II was unable to demonstrate any benefit of warfarin over aspirin in very elderly patients, critics of SPAF II have pointed out the following: (1) the “therapeutic range” of warfarin was excessively wide; (2) the prothrombin time (PT) ratio rather than the international normalized ratio (INR) was initially utilized; and (3) patients were often not successfully maintained within the therapeutic range.

**Physician Attitudes**

If outcome data from randomized controlled trials are applied to clinical practice, then anticoagulation is underutilized. Stafford and Singer analyzed 1,062 visits by patients with AF randomly selected from a national database. Warfarin use increased significantly between 1980 and 1993, but even in the latter year, only 37% of patients with AF were taking warfarin. In addition, patients aged ≥80 years were significantly less likely to be taking warfarin in 1992 and 1993 than younger patients (19% vs 36%). Thus, many physicians are reluctant to apply the results of the AF trials and, even prior to the publication of SPAF II in 1994, physicians were particularly reluctant to provide anticoagulation for the very elderly.

More recently, Gurwitz et al surveyed the records of 30 long-term care facilities in New England, Quebec, and Ontario between 1993 and 1995 and documented AF in 413 of 5,500 long-term care residents (7.5%), 91% of whom were ≥75 years of age. Overall, 32% of such patients were being treated with warfarin, while 25% were being treated with aspirin alone, 0.5% with both, and 42% with neither. Patients with a history of stroke were 60% more likely to be treated with warfarin. Interestingly, AF patients with a history of bleeding were as likely to undergo anticoagulation as other AF patients, and 28% of patients with AF who had undergone anticoagulation had a history of falls. Finally, this study documented relatively poor quality of anticoagulation compared with the published AF trials. Patients who had undergone anticoagulation were found to be subtherapeutic 45% and supertherapeutic 16% of the time that INRs were checked.

**Current Status**

The principal problem is that those very elderly AF patients at highest risk for ischemic stroke are also at highest risk for intracranial hemorrhage. In most AF trials, intracranial bleeding occurred at an average INR of only 3.5. Initial hope that low-dose anticoagulation therapy (target INR, 1.5 to 1.9) might be as effective as standard therapy (INR, 2.0 to 3.0) has been dispelled by two recent studies showing that patients suffering ischemic stroke while taking warfarin for AF were significantly more likely to have had an INR <2.0 at the time of their stroke. Furthermore, the recently published SPAF III study demonstrated that low-intensity warfarin combined with aspirin was ineffective in stroke prevention.

A physician who decides to provide anticoagulation for a very elderly patient with AF faces several challenges. He or she must provide high-quality INR monitoring comparable to that of major clinical trials. Such monitoring is potentially time-consuming, tedious, and usually uncompensated. The physician also faces the burden of carefully selecting patients at low risk of bleeding. It is noteworthy that most patients with AF evaluated for entry into randomized trials were excluded, suggesting that only ideal, “cream of the crop” anticoagulation candidates were allowed into these trials. Finally, the clinician prescribing warfarin to an elderly patient must accept a small but real chance that he or she will thereby precipitate a major bleeding event, thus violating the principle of *primum non nocere* that runs so deeply in medical culture.
Given these concerns, how should one approach a patient with chronic AF who is >75 years old? Successful cardioversion will eliminate the long-term stroke risk without the hazards of extended anticoagulation and will often improve hemodynamics.

If cardioversion is unsuccessful or contraindicated and the patient remains in chronic AF, the clinician must confront the difficult decision about warfarin. Rather than providing anticoagulation for all patients >75 years old, we advocate a more judicious approach in which all risk factors for ischemic stroke and major bleeding are carefully considered and balanced. Additional risk factors for stroke in patients with AF include left atrial enlargement, left ventricular dysfunction, hypertension, diabetes mellitus, male gender, valve disease, and prior transient ischemic attack or stroke. Most AF patients >80 years have at least one of these risk factors. Presence of an increasing number of risk factors in addition to AF should weigh in favor of anticoagulation, while relative contraindications and bleeding risks, such as prior intracranial hemorrhage, prior GI bleeding, coagulopathy, nonsteroidal anti-inflammatory drug use, dementia, and a history of frequent falls, should weigh against anticoagulation. Balancing these risks requires the art as well as the science of medicine.

If the risk-benefit assessment is against anticoagulation, physicians should still strongly consider treatment with aspirin, which reduces stroke risk in chronic AF. Aspirin has obvious advantages over warfarin in safety, ease of administration, and low cost, and may be a superior choice in many very elderly patients.

If warfarin is chosen for stroke prophylaxis, then several precautions should be observed. The patient and family should understand the rationale, risks, and shared responsibility inherent in long-term warfarin use. The clinician should double-check logistical arrangements for phlebotomy, laboratory assay, and reporting results. Ideally, the patient should be followed up in a well-organized anticoagulation clinic. Good communication between specialists and primary care physicians is imperative, as a treatment decision (such as starting treatment with a new medication or scheduling surgery) made by any member of the health-care team can affect the warfarin management plan. Most importantly, a single physician must be identified as primarily responsible for a given patient’s warfarin management, lest multiple providers each assume the other is responsible.

Common sense precautions should be taken to prevent falls at home. Visiting nurses can evaluate home safety to check for obvious hazards. Many elderly patients must arise several times at night to use the bathroom, and nightlights can thus be helpful. A gait assessment should be performed to determine whether a cane or walker is needed. Dietary advice should focus on maintaining a consistent, well-balanced diet. We find that proscribing or limiting certain foods is unnecessarily confusing and rarely helpful in warfarin management. Some elderly patients do little cooking for themselves and live on a “tea and toast” subsistence. For them, referral to a community nutrition resource such as Meals-on-Wheels can be invaluable.

Regular assessment of compliance is an essential part of any patient’s warfarin management, particularly in the very elderly patient. Ideally, pill bottles should be brought in and reviewed at each office visit. We favor the prescription of Coumadin, which has had a long history of reliable bioavailability and safe manufacturing, rather than recently introduced generic warfarin. When assessing compliance and making dosage changes over the phone, clinicians need to be familiar with the color coding of Coumadin tablets, as many patients understand their dosing only by this means and not in terms of milligrams. For certain patients, a 7-day pill box filled weekly by a visiting nurse may offer the best solution. Attention to such details may seem mundane and trivial; however, in an elderly patient taking a medication with such a narrow therapeutic index, such details can make the difference between successful stroke prevention and disastrous hemorrhagic complications.

**Future Directions**

More than 1 million Americans >75 years old currently have AF, and this number will increase dramatically in the coming decades as the population ages. Low utilization of aspirin or warfarin in elderly patients suggests that many physicians remain unconvinced of the value of either therapy in this age group. What is most urgently needed is a large, well-designed, randomized trial comparing warfarin (target INR, 2.0 to 3.0) with aspirin (325 mg daily) in patients >75 years old with AF. A well-designed trial looking specifically at the very elderly has the potential to answer the question definitively and might pay for itself many times over in reduced medical and nursing costs for thrombotic or hemorrhagic stroke patients.

Methods for easier monitoring of the anticoagulant response will increase the safety and prevalence of warfarin use in appropriate patients. There already exist devices for immediate measurement of the PT and partial thromboplastin time from a fingerstick blood sample, and the Food and Drug Administration has just approved several PT/INR...
devices for home use. The availability of anticoagulation clinics should increase use of warfarin in appropriate patients by relieving the prescribing physician of many difficult and time-consuming details and ensuring closer follow-up and better compliance with the prescribed target INR. Furthermore, by following up large cohorts of patients who have undergone anticoagulation, anticoagulation clinics will serve as natural centers of research into risk factors for major bleeding and treatment failure.

In the interim, physicians caring for very elderly patients with AF will continue to face the challenging task of complex individualized risk-benefit analysis based on limited information. Cardioversion should be considered in most cases. For patients remaining in chronic AF, the current literature supports using either warfarin to a target INR of 2.0 to 3.0, or aspirin 325 mg daily, depending on individual circumstances. Only unusual patients with definite contraindications to both medications should go without any stroke prophylaxis. Very elderly patients taking warfarin merit special precautions and careful follow-up. Future research should provide better information on optimal stroke prophylaxis in this important and expanding group of patients.

REFERENCES
1 White HD. Aspirin or warfarin for non-rheumatic atrial fibrillation? Lancet 1994; 343:683-84