Growing old is like being increasingly penalized for a crime you haven’t committed.
—Anthony Powell, Temporary Kings

Anticoagulation therapy for thromboembolism prophylaxis in patients with atrial fibrillation (AF) is based on quality information derived from numerous randomized controlled trials but continues to be a conundrum for many physicians. The AF treatment guidelines have been revised recently, but new information is emerging at such a rapid rate that it is hard to imagine how the guideline process can keep up with the pace. In this issue of the journal, there is new and rather startling information derived from careful observation of the initiation of warfarin therapy in a cohort of elderly patients with AF. Several aspects of this study deserve emphasis.

**Article p 2689**

**Key Points from Hylek et al**

The subjects in the cohort of Hylek et al possess some unique characteristics. The obvious one is the age of the patients. All were aged ≥65 years. It is equally notable that none of them had been on warfarin during the preceding year. A substantial proportion of women were included in the cohort. Among those aged ≥80 years, 55% were women. It is also notable that the duration of follow-up was restricted to the first year of warfarin therapy.

The most obvious finding to be emphasized is the high proportion of serious bleeding incidents. The reported amount of major bleeding during use of vitamin K antagonists over nearly 2 decades has varied (see Table 4). There is, however, a discernible pattern over time. In general, less major bleeding was reported in older studies than in recent studies. A pooled analysis of the original major randomized controlled trials of anticoagulation for thromboembolism prophylaxis in AF patients reported an annual rate of major hemorrhage of 1.3% in 1994. However, it is rare that this low level of risk has been replicated in contemporary studies, and then perhaps only in patients who are stable on long-term anticoagulation.

Thus, the second finding to be emphasized from Hylek et al is the enhanced risk of bleeding in patients while starting anticoagulation therapy. This phenomenon, although known, has been underappreciated by many clinicians. Table 4 of Hylek et al clearly illustrates that the risk of major bleeding in an inception cohort is considerably higher than that found in the pooled analysis of the original 5 randomized clinical trials from 1994 and in noninception cohort studies. The enhanced risk of bleeding while starting anticoagulation has also been found in contemporary randomized controlled trials. The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W) noted a risk of major bleeding at the end of the first year of ~4% in warfarin-experienced patients and 6% to 7% in warfarin-naive patients.

Finally, Hylek et al reported that patients with a greater need for antithrombotic therapy, based on the CHADS2 (congestive heart failure, hypertension, age, diabetes, stroke) risk stratification scheme, also have greater risk of bleeding. The risk of major hemorrhage may increase by a factor of 10-fold between CHADS2 scores of 0 and ≥4. This finding poses a real and important challenge for effective and safe anticoagulation for high-risk patients with AF.

**Exploring the Key Points From Hylek et al**

Limiting the duration of follow-up has an impact on the estimate of bleeding rate. The rate of bleeding in the first year is higher than the annual risk of bleeding amortized over a longer period of time. One of the main reasons for the decreased risk after the first year is discontinuation of therapy by high-risk patients after a bleeding event. In ACTIVE W, the annual risk of major hemorrhage over the duration of the study is quoted as 2.6% and 2.0% for warfarin-naïve and warfarin-experienced patients, respectively. In contrast, the risks are more like 6% to 7% and 4%, respectively, in the first year. It makes a difference in discussions with patients whether they are provided with an estimate of risk for the first year or an estimate of annual risk over a longer period of time. The report of Hylek et al does not provide an estimate of risk beyond the first year of therapy.

It would be useful to understand factors contributing to the increased risk of bleeding reported in contemporary compared with older studies. One obvious consideration is the definition of major hemorrhage. Has it changed over the
years? When one examines the definitions of major hemorrhage in the various studies, minor variations can be observed but no substantial differences. It is unlikely, therefore, that contemporary reports of a higher rate of major hemorrhage can be explained by differences in definition.

Accordingly, the higher rate of bleeding now being reported probably has other explanations. Is it a real increase or an apparent increase? It is difficult to answer this question without knowing more about the comparability of the patients enrolled in different time periods. Differences undoubtedly exist in the patients themselves, but published information on all the potentially relevant characteristics is limited.

The increasing risk of bleeding with increasing age is clearly demonstrated in the study of Hylek et al (average age was 77 years). Are patients enrolled in contemporary studies older? Variation in age certainly exists in the various studies (see Table 4 in Hylek et al). However, the average age in ACTIVE W, for example, is 70 years compared with an average age of 69 years in the pooled analysis of the original 5 randomized controlled trials from 1994. Therefore, age would not seem to be an explanation for the differences in bleeding risk between ACTIVE W and the original 5 trials.

The risk of bleeding in patients with AF being treated with warfarin has been reported to be greater in women than in men in the Framingham Heart Study. This gender-based difference in risk persists after adjustment for age. Adjustment for age is important because the proportion of women in AF cohorts increases with increasing age of the cohort (see, for example, Hylek et al). The proportion of women in contemporary randomized controlled trials of AF therapy is usually ≈45%. In the original 5 randomized controlled trials of warfarin prophylaxis in AF patients, the proportion of women enrolled was only ≈25%. Thus, a greater risk of bleeding in more recent studies may be due in part to the enrollment of more women.

Other potential explanations for the differences in bleeding in earlier versus contemporary studies are more speculative. Details about key information are often not provided in the published articles. It may be that earlier trialists were particularly concerned about bleeding and used stricter exclusion criteria based on bleeding risk. Certainly, it seems likely that the concomitant use of antiplatelet agents, which increase the risk of bleeding, is much more prevalent now. Concomitant use of warfarin and antiplatelet agents occurs particularly in those with ischemic heart disease, and they represent approximately one third of patients in contemporary randomized controlled trials of AF therapies (see, for example, Reference 4).

The observation of a greater risk of bleeding in patients with higher CHADS2 scores is particularly troubling. Formal systems are available for assessing risk of bleeding, but they are not as widely known or used as the scoring systems for assessing the risk of thrombotic stroke. Evidently, a great deal of overlap exists in thrombotic stroke risk and risk of bleeding. Such overlapping risk creates a difficult management problem. Whether the needs of high-risk patients can be met by newer pharmacological and nonpharmacological antithrombotic/embolic therapies remains to be determined.

Other Comments on Hylek et al

The revised 2006 guidelines for management of patients with AF, compared with those of 2001, are less enthusiastic about recommending use of warfarin, presumably because of a reevaluation of the benefit/risk of anticoagulation. On the benefit side, the risk of thrombotic stroke in AF patients appears to be declining. Two potential explanations for such a decline in more recent studies are better control of hypertension and inclusion of more patients with paroxysmal AF.

On the risk side, increased appreciation of the risk of bleeding has been discussed above.

Hylek et al introduce their study by commenting on “underutilization” of warfarin in patients with AF. The term underutilization implies that a decision not to use warfarin is reached after assessment of the balance between benefit (prevention of thrombotic stroke) and risk (bleeding) suggests a net benefit. Given the demonstrated risk of major bleeding in Hylek et al, there is reason to be skeptical about net benefit when warfarin is used in some elderly patients with AF.

Hylek et al planned and completed their study before the publication of the new guidelines. In Table 1, 13% of their patients aged <80 years had a CHADS2 score of 0, for which the current guidelines would recommend aspirin alone. Another 26% of their patients (33% in those aged ≥80 years) had a CHADS2 score of 1, for which the current guidelines would recommend either aspirin or warfarin. Considering the apparent declining risk of thrombotic stroke and the reported risk of bleeding here, one might consider use of warfarin in this 39% of the patients in the Hylek et al report as a relative overutilization, unless it was done temporarily for cardioversion, for example. Overutilization of warfarin in patients at low risk of thrombotic stroke is also demonstrated in the Euro Heart Survey on Atrial Fibrillation. Even with the use of the more strict 2001 guidelines, they reported that 50% of AF patients without stroke risk factors were being treated with vitamin K antagonists.

Hylek et al note increased risk of major bleeding events when the international normalized ratio (INR) is >4.0. The important relationship of the INR to the risk of bleeding has been reported previously by these authors, emphasizing the increased risk in the elderly when the INR was ≥3.5. The importance of carefully regulating the INR in the elderly cannot be overemphasized. When warfarin is used in the elderly, the INR probably needs more frequent and careful monitoring.

Moving Forward

A need exists for reexamination, consolidation, and simplification of scoring systems for assessment of contemporary stroke risk in patients with AF. It would also be extremely useful if one were able to estimate a net benefit comparing the risk of bleeding and the risk of thrombotic stroke. The most difficult obstacle to a net benefit scheme is agreement about a hierarchy for comparing stroke and bleeding events. A thrombotic stroke with a residual Rankin Scale score of 0 or 1 is not equivalent to a thrombotic stroke with a residual Rankin Scale score of 4 or 5. It is possible with the use of Rankin scores to compare thrombotic and bleeding strokes, although comparing other major bleeding events with throm-
botic strokes is not as easy. Furthermore, it would be useful to make a separate risk assessment for the first and subsequent years, for paroxysmal and nonparoxysmal AF, and for male and female gender.

Current and recently completed trials comparing vitamin K antagonists with antiplatelet agents, oral thrombin inhibitors, or oral and subcutaneous factor Xa inhibitors will enroll >50,000 patients. Of those, 35% to 40% will be treated with vitamin K antagonists. ACTIVE A11 will also enroll ≈4000 patients eligible for vitamin K antagonists who have a contraindication to such therapy or refuse it and treat them with aspirin alone. It seems, therefore, that there will soon be an opportunity to repeat a pooled analysis, as was done by the Atrial Fibrillation Investigators3 more than a decade ago, to provide a contemporary assessment of risk of stroke, with and without anticoagulation, and risk of bleeding on vitamin K antagonists. Such an opportunity should not be missed.

**Disclosures**

The author reports having received research grants from Cardiome/Astellas and Medtronic. He has served on scientific advisory boards for Boehringer Ingelheim, Cardiome/Astellas, CV Therapeutics, Medtronic, Novartis, and Sanofi-Aventis and has been a speaker for Cardiome/Astellas and Eisai Pharma (all <$10 000).

**References**


**KEY WORDS:** Editorials anticoagulants arrhythmia prevention stroke
Bleeding While Starting Anticoagulation for Thromboembolism Prophylaxis in Elderly Patients With Atrial Fibrillation: From Bad to Worse

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_Circulation_. 2007;115:2684-2686
doi: 10.1161/CIRCULATIONAHA.107.704122

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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