

Anticoagulant-Related Bleeding in Older Persons With Atrial Fibrillation

Physicians' Fears Often Unfounded

Malcolm Man-Son-Hing, MD, MSc; Andreas Laupacis, MD, MSc

Background: Many studies have documented the underuse of anticoagulant (ie, warfarin sodium) therapy as stroke prophylaxis in older persons with atrial fibrillation. Failure to prescribe anticoagulant agents to these patients is often due to physicians' perceiving the risk of major bleeding as unacceptably high because of the presence of such clinical risk factors as hypertension, falls, a history of gastrointestinal tract bleeding, and lack of assurance about compliance.

Objectives: To critically appraise whether the presence of additional clinical factors that increase the risk of bleeding affects the chance of anticoagulant-related hemorrhage, and to develop an approach to the use of anticoagulant agents in older patients with atrial fibrillation who have any of these factors.

Methods: Systematic MEDLINE literature search from January 1966 to March 2002.

Results: Many of the factors that are purported to be barriers to anticoagulant therapy in older persons with atrial

fibrillation probably should not influence the choice of stroke prophylaxis in these patients. These include previous episodes of upper gastrointestinal tract bleeding, predisposition to falling, and old age in itself. For some other factors, such as alcoholism, participation in activities that predispose to trauma, the presence of a bleeding diathesis or thrombocytopenia, and noncompliance with monitoring, there is little or conflicting evidence about their effect on anticoagulant-related bleeding. However, they should be considered in the clinical decision-making process.

Conclusions: For many older patients with atrial fibrillation, physicians' fears of the risk of bleeding in association with anticoagulant therapy are often exaggerated and unfounded. Therefore, the salient issue in selecting older patients with atrial fibrillation for anticoagulation is accurately estimating their stroke risk, with bleeding risk during anticoagulation being a lesser issue, relevant to only a few patients.

Arch Intern Med. 2003;163:1580-1586

From the Clinical Epidemiology Program, Ottawa Health Research Institute; Geriatric Assessment Unit, Ottawa Hospital; Division of Geriatric Medicine, University of Ottawa; and Institute on Health of the Elderly, Sisters of Charity Ottawa Health Service; Ottawa (Dr Man-Son-Hing); and the Institute for Clinical Evaluative Sciences and Faculty of Medicine, University of Toronto, Toronto (Dr Laupacis); Ontario, Canada. The authors have no relevant financial interest in this article.

APPROXIMATELY 5% of persons older than 65 years have atrial fibrillation (AF), the most common cardiac arrhythmia.¹ Older persons with AF are at increased risk of thromboembolic stroke, ranging from 4% to 15% per year,² depending on the presence of certain clinical factors, including left ventricular dysfunction, a history of hypertension, a history of stroke or transient ischemic attack, diabetes mellitus, and increasing age.^{2,3} Multiple randomized controlled trials have demonstrated that the use of long-term antithrombotic therapy with anticoagulant agents (ie, warfarin sodium) and aspirin reduces the relative risk of stroke from AF by approximately 65%^{4,5} and 20%,^{4,6} respectively. Moreover, some studies⁷⁻⁹ have shown that stroke prophylaxis with anticoagulant agents is cost-effective, especially in older

persons. Therefore, an expert panel recommended that all persons with AF who are older than 75 should be considered for chronic anticoagulation unless a contraindication exists.²

However, there can be significant disadvantages to anticoagulant therapy, including cost, inconvenience (eg, regular blood monitoring), and, most important, an increased risk of potentially life-threatening bleeding complications. In association with anticoagulant therapy, other clinical risk factors may increase the overall chance of bleeding (eg, poor compliance with medications¹⁰) and bleeding into specific locations (eg, gastrointestinal [GI] tract bleeding with the use of nonsteroidal anti-inflammatory drugs [NSAIDs]¹¹ and intracranial bleeding with uncontrolled hypertension¹²). Therefore, it is not surprising that many physicians are reluctant to prescribe anticoagulant therapy

for patients in the presence of 1 or more of these risk factors.¹³ The objective of this study was to critically appraise whether the presence of additional clinical risk factors for bleeding affects the chance of anticoagulant-related hemorrhage. Then, based on these findings, a clinical approach to the appropriate use of anticoagulant agents in older patients with AF in the presence of any of these factors is outlined.

METHODS

We reviewed and summarized the evidence pertaining to whether the following factors increased the chance of anticoagulant-related major bleeding:

1. Gastrointestinal tract bleeding risk factors: history of peptic ulcer bleeding and the concomitant use of conventional (with or without cytoprotection) or cyclooxygenase-2 inhibitor–specific NSAIDs;
2. Intracranial bleeding risk factors: uncontrolled hypertension, predisposition to falls with head trauma, participation in activities with a high risk of head injury, and previous stroke;
3. General bleeding risk factors: inability to adequately regulate international normalized ratio (INR) status because of aging, the presence of a bleeding diathesis or thrombocytopenia, alcoholism, poor compliance with medications, and increased bleeding in the very old.

Relevant data were gathered by performing systematic literature searches using the MEDLINE (January 1966 to March 2002) computerized database. Literature searches performed in 2 earlier studies^{14,15} examining the effect of GI tract bleeding and risk for falls on the choice of appropriate antithrombotic therapy in older patients with AF formed the basis of the data gathering. These searches were updated to March 2002, with further pertinent articles identified by using the following keywords (human only): *anticoagulants, cerebral hemorrhage, subdural hematoma, warfarin, atrial fibrillation, stroke, alcohol(ism), international normalized ratio, bleeding diathesis, thrombocytopenia, platelets, elderly, outcome assessment (health care), treatment outcome, prognosis, and risk factors*. The bibliographies of each identified, possibly pertinent article were reviewed to identify additional articles. Content experts were consulted to identify other relevant published works. If available, articles that quantitatively reviewed pertinent topics were favored.

We then asked 4 physicians (2 internists and 2 family physicians) to independently judge the effect that each bleeding risk factor should have on the decision whether to initiate anticoagulant therapy. Based on the synthesis of the gathered information and the physicians' recommendations, we then developed an algorithm to guide physicians in determining the appropriate antithrombotic therapy for older patients with AF in the presence of these factors.

RESULTS

GI TRACT BLEEDING RISK FACTORS

Using decision-analytic modeling, a recent study¹⁴ analyzed how factors that increase the risk of major upper GI hemorrhage influence the choice of antithrombotic therapy in older patients with AF. Based on a review of the literature and analysis,¹⁴ it was concluded that, in the era of routine testing and treatment for *Helicobacter pylori*, persons with spontaneous (ie, non-NSAID related) upper GI tract bleeding episodes are not at a signifi-

cantly increased risk of a recurrent bleeding episode once the initial episode has resolved.¹⁶⁻¹⁸ Therefore, persons who have had a resolved upper GI tract bleeding episode appear to be at no further increased risk of upper GI tract bleeding compared with persons without a history of upper GI tract bleeding.

A comprehensive meta-analysis¹⁹ determined that, for persons taking conventional NSAIDs without cytoprotection, the increased risk of GI tract bleeding was 3.8 (95% confidence interval [CI], 3.6-4.1) times that of control subjects. The concomitant use of misoprostol or a proton pump inhibitor with conventional NSAIDs reduced this risk by 50%.^{20,21} Similarly, the use of a cyclooxygenase-2 inhibitor–specific NSAID reduced the risk of upper GI tract bleeding to about half that associated with a conventional NSAID.²²

In the previously mentioned study,¹⁴ antithrombotic treatment recommendations were derived (**Table 1**) based on the risk of upper GI tract bleeding and stroke using a multiplicative approach to determine the risk of anticoagulant-related bleeding in the presence of these risk factors (eg, 3.8 times baseline when taking conventional NSAIDs and 2.4 times baseline when taking warfarin⁴; therefore, when taking both, the risk is 9.1 [3.8 × 2.4] times baseline). For almost all scenarios analyzed, warfarin was the optimal therapy (in terms of number of quality-adjusted life-years gained) for most older persons with AF. The main exception was persons having a low risk of stroke from AF (ie, no clinical risk factors that increase their chance of stroke) and a high risk of upper GI tract bleeding (ie, taking conventional NSAIDs). In this situation, aspirin, or no antithrombotic therapy, is a reasonable option.

INTRACRANIAL BLEEDING RISK FACTORS

Multiple studies²³⁻²⁵ have documented an increased rate of intracerebral hemorrhage in persons with uncontrolled hypertension who are not taking anticoagulant agents. For example, Saloheimo et al²³ found that persons whose blood pressure was higher than 160/95 mm Hg were much more likely to have an intracerebral hemorrhage compared with those with lower blood pressures (odds ratio, 7.0; 95% CI, 3.1-15.8). Even persons with treated hypertension had an increased risk (odds ratio, 2.7; 95% CI, 1.0-6.9).²³ Other studies²⁶⁻³² have shown that the presence of hypertension increases the risk of intracerebral hemorrhage in persons taking anticoagulant agents. For example, the Stroke Prevention in Atrial Fibrillation investigators³² found that systolic (≥ 160 mm Hg) and diastolic (≥ 90 mm Hg) hypertension conferred additional risk of anticoagulant-related intracerebral hemorrhage (relative risk, approximately 4). Therefore, in older persons with significant hypertension (systolic, ≥ 90 mm Hg; or diastolic, ≥ 160 mm Hg), it is reasonable clinical practice to delay the initiation of anticoagulant therapy until treatment lowers their blood pressure consistently below these levels.

It is clear that persons who experience head trauma have an increased likelihood of developing intracranial bleeding³³⁻³⁶ (especially subdural hematomas), and this risk is increased in persons taking anticoagulant agents.³⁷⁻⁴³

Table 1. Stroke Prophylaxis Treatment Recommendations, Based on Maximizing QALYs*

Variable	Risk of Upper GI Tract Bleeding, %/y	Risk of Stroke, %/y†	QALYs			Antithrombotic Treatment Recommendations	General Recommendations		
			Warfarin Therapy	Aspirin Therapy	NT				
Recent resolved GI tract bleeding (with <i>Helicobacter pylori</i> testing and treatment)									
Aged 65-75 y‡									
No RF	1.2	4.3	11.13	10.52	10.12	Warfarin	None		
≥1 RF		5.7	10.68	9.70	9.18	Warfarin			
Aged >75 y§									
No RF		4.3	8.08	7.71	7.47	Warfarin			
≥1 RF		8.1	7.36	6.43	6.02	Warfarin			
Concurrent NSAID and misoprostol or PPI use or COX-2-specific NSAID use									
Aged 65-75 y‡									
No RF	2.3	4.3	10.75	10.35	9.98	Warfarin	None		
≥1 RF		5.7	10.27	9.55	9.06	Warfarin			
Aged >75 y§									
No RF		4.3	7.84	7.60	7.39	Warfarin or aspirin			
≥1 RF		8.1	7.09	6.35	5.96	Warfarin			
Concurrent conventional NSAID use									
Aged 65-75 y‡									
No RF	4.5	4.3	10.12	10.02	9.71	Warfarin or aspirin	Assess the need for NSAIDs, consider a switch to an alternative analgesic, and consider the addition of misoprostol or PPIs		
≥1 RF		5.7	9.62	9.25	8.82	Warfarin			
Aged >75 y§									
No RF		4.3	7.44	7.39	7.21	Warfarin, aspirin, or NT			
≥1 RF		8.1	6.66	6.19	5.83	Warfarin			

Abbreviations: COX-2, cyclooxygenase-2; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; NT, no antithrombotic therapy; PPI, proton pump inhibitor; QALY, quality-adjusted life-year; RF, risk factor for stroke from atrial fibrillation, including previous stroke or transient ischemic attack, history of hypertension, left ventricular dysfunction, and possibly diabetes mellitus. Warfarin was given as warfarin sodium.

*Reprinted with permission.¹⁴

†Data from Atrial Fibrillation Investigators.⁶

‡Start age of 70 years.

§Start age of 80 years.

However, it is unclear whether this risk is sufficient to influence clinical decision making in older persons with AF. For example, a recent decision analysis¹⁵ concluded that a predisposition to falls (with possible head trauma) is not a contraindication to the use of anticoagulant agents in older patients with AF. Even when taking anticoagulant agents, the risk of subdural hematoma from falling is so small that persons with an average risk of stroke from AF (5% per year) must fall approximately 300 times in a year for the risks of anticoagulant therapy to outweigh its benefits.¹⁵

Participation in recreational activities with an increased chance of head trauma (eg, skydiving, downhill skiing, and rollerblading) may increase the risk of anticoagulant-related intracranial bleeding. Although recognizing that few older persons participate in such activities, there is no information from published studies to help quantify these risks. Therefore, until these bleeding risks are further defined, it is difficult to give specific recommendations about the use of anticoagulant agents in persons participating in these activities. Some of these activities would seem to pose greater risks than others, with decisions about anticoagulant therapy needing to be made on an individual basis, using clinical judgment.

Previous investigations,⁴⁴ done at a time when the intensity of anticoagulation was higher than is the norm presently, documented a higher than expected rate of in-

tracerebral hemorrhage in persons with previous stroke who were taking anticoagulant agents. More recently, this finding was confirmed when a study⁴⁵ found that the rate of intracerebral hemorrhage in patients taking warfarin (target INR, 3.0-4.5) after a recent transient ischemic attack or minor stroke was unacceptably high. With the present use of less intense anticoagulation regimens (target INR, 2.0-3.0), more recent studies^{46,47} have not confirmed this finding. Given that previous stroke substantially increases the risk of a recurrent stroke in persons with AF,⁶ a history of stroke should not be considered a contraindication to anticoagulant therapy.

GENERAL BLEEDING RISK FACTORS

No studies were found that examined whether there is an incremental increased risk of anticoagulant-related bleeding in persons who have a bleeding diathesis. This probably relates to the reluctance and infrequency with which these persons are prescribed anticoagulant agents. With regard to thrombocytopenia, bleeding is infrequent even after minor procedures, such as liver biopsy, in persons with platelet counts of more than $50 \times 10^3/\mu\text{L}$.^{48,49} A platelet count of $20 \times 10^3/\mu\text{L}$ or less has been the traditional threshold for use of prophylactic platelet transfusions, with the recent trend to withholding therapy

to levels as low as $10 \times 10^3/\mu\text{L}$.⁵⁰ However, among patients taking anticoagulant agents, it is unclear from the literature whether $50 \times 10^3/\mu\text{L}$ or lower levels of thrombocytopenia confer unacceptably high risks of bleeding. With little empirical information to guide decision making in these clinical situations, it seems prudent to avoid anticoagulant agents in persons with bleeding diatheses or platelet counts of $50 \times 10^3/\mu\text{L}$ or lower.

Through the mechanisms of falls with subsequent development of subdural hematomas, predisposition to gastropathy, and direct effects on coagulation and liver metabolism, persons who abuse alcohol may be prone to anticoagulant-related hemorrhagic complications. It could also be surmised that these persons may be less compliant with anticoagulant dosing and INR monitoring. Based on retrospective medical chart reviews of physician documentation of a history of alcohol abuse, 4 studies⁵¹⁻⁵⁴ found that alcohol abuse predisposes persons to higher than normal rates of anticoagulant-related bleeding. In these studies, the relative risk of major bleeding in these patients was approximately 2.6 times the baseline rate. Other retrospective studies⁵⁵⁻⁵⁷ have not found this association but have been criticized for possible inaccuracies in medical chart documentation and the infrequent use of anticoagulant therapy in these patients.⁵⁸ In fact, one study⁵⁹ in which patients with INR values higher than 6.0 were interviewed found alcohol use to be protective (relative risk, 0.6) of major bleeding. An obvious limitation of these studies (except for the study by Hylek et al⁵⁹) is the use of subjective physician judgment and the nonsystematic documentation to define and identify persons with alcohol abuse. A limited survey of physicians suggested that most caution their patients who are taking warfarin about the dangers of using alcohol concurrently but allow them to have 30 mL, or perhaps 60 mL, of alcohol per day.⁶⁰ Therefore, given this conflicting and possibly unreliable information, it would seem prudent to have assurances of alcohol intake of a maximum of 2 drinks per day before initiation of anticoagulant therapy.

Several studies⁶¹⁻⁶³ have shown that the intensity of anticoagulation is strongly correlated with the development of anticoagulant-related bleeding. International normalized ratio levels well above the therapeutic range (INR, >4.0) are associated with dramatic increases (up to 7-fold) in the risk of intracerebral bleeding.²⁶ Poor compliance with anticoagulant agents or INR monitoring has been shown to increase the risk of INRs above the therapeutic range.⁵² Therefore, poor compliance with anticoagulant agents or INR monitoring is likely to substantially increase the risk of anticoagulant-related bleeding. Until compliance with the taking of medication and INR monitoring can be assured, it is prudent that anticoagulant therapy be withheld. Similarly, anticoagulant agents should be discontinued in patients who have poor compliance with medications.

There has been some reluctance to offer anticoagulant therapy to older patients with AF because of the perceived inability to adequately regulate INR status because of aging.⁶⁴ Hylek et al⁶⁵ studied 4517 outpatients who were taking warfarin for AF, with most managed by their primary care physicians. The authors reviewed the quality of INR control according to age by measuring time in the therapeutic range (INR, 2.0-3.0), at an INR above 5.0, and at an INR below 1.5. They found no difference

Additional Risk Factors (Age >65 y Is a Risk Factor in Itself)	
<ul style="list-style-type: none"> • History of Hypertension • Left Ventricular Dysfunction (History of Congestive Heart Failure or Echocardiography Findings) • Previous Transient Ischemic Attack or Stroke (Automatically in the 10%-12% [Very High] Risk Category) • Diabetes Mellitus 	
Additional Risk Factors	Yearly Chance of Stroke, %
≥2	10-12 (Very High)
1	7-8 (High)
0	4-5 (Medium)

Assessment of stroke risk in older persons with atrial fibrillation.

among age groups younger than 65, 65 to 74, 75 to 84, and older than 84 years in the percentage of time in the therapeutic range or well above and below the therapeutic range. Therefore, it does not appear to be more inherently difficult to maintain INRs in the therapeutic range as persons get older.

Although some studies^{37,53,66} have confirmed that there is an increased risk of anticoagulant-related upper GI tract bleeding in persons older than 65, compared with those 65 and younger, it is unclear whether there continues to be a gradient of increased risk as those older than 65 grow older. The Stroke Prevention in Atrial Fibrillation II study⁶⁷ found that the gradient of warfarin-related major bleeding risk was independently and significantly related to age, continuing to rise past age 75. These results have been questioned because of the use of anticoagulation intensity that is higher than what is used presently (INR, 2.0-4.5) and the small number of bleeding events.⁵² Also, Beyth and Landefeld⁶⁸ found that the odds ratio for anticoagulant-related bleeding was 1.7 (95% CI, 1.0-2.8) for patients aged 65 to 74 years and 3.0 (95% CI, 1.7-5.1) for those 75 and older, compared with a referent population 64 and younger. Other studies^{57,69} have found no association between anticoagulant-related bleeding and age, although they have been criticized for possible biases, including the use of non-inception cohorts (ie, some patients had been taking anticoagulant agents before the study, so those at the highest risk of bleeding were selected out). Finally, the sensitivity analysis of the study¹⁴ that examined the effect of GI tract bleeding risk factors on the choice of antithrombotic therapy showed that a clinically plausible increased risk of bleeding in patients older than 75 did not influence the choice of antithrombotic therapy in this age group. Therefore, when deciding whether to institute anticoagulant therapy in this age group, it is likely that any increased risk of bleeding is offset by an increased risk of stroke that increasing age confers.

APPROACH TO ANTICOAGULANT THERAPY IN OLDER PATIENTS WITH AF

Assess Stroke Risk

The most salient issue when deciding whether older persons with AF should receive anticoagulant agents is their stroke risk. The **Figure** outlines a risk stratification scheme for older persons, based on the presence of clinical risk factors that increase the chance of stroke.^{3,5,7,70}

Table 2. Assessment of Bleeding Risk in Older Persons With Atrial Fibrillation

Condition	Contraindication Regarding Warfarin Sodium Use	Grade of Recommendation*	Level of Evidence†
Bleeding diathesis	Absolute	C	III
Thrombocytopenia (<50 × 10 ³ /μL)	Absolute	C	II-2
Untreated or poorly controlled hypertension (consistently >160/90 mm Hg)	Absolute	B	II-2
Noncompliance with medication or INR monitoring	Absolute	B	II-2
Significant alcohol use (>60 mL/d)	Relative	C	II-2
Conventional NSAID use (without cytoprotection)	Relative	B	II-3
Participation in activities predisposing to trauma	Relative	B	III
Predisposition to falling	No	B	II-3
Perceived inability to adequately control INR status because of age	No	A	II-2
Conventional NSAID use with misoprostol or proton pump inhibitor	No	A	II-3
Cyclooxygenase-2 inhibitor–specific NSAID use	No	A	II-3
Recent, resolved peptic ulcer disease bleeding (with <i>Helicobacter pylori</i> testing and treatment)	No	A	II-2
Previous stroke	No	A	I

Abbreviations: INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug.

*Grades of recommendations (adapted from Canadian Task Force on Preventive Healthcare⁷¹): A, good evidence to support the recommendation; B, fair evidence to support the recommendation; and C, poor evidence, but recommendations may be made on other grounds.

†Quality of published evidence (adapted from Canadian Task Force on Preventive Healthcare⁷¹): I, evidence from at least 1 properly randomized controlled trial; II-1, evidence from well designed controlled trials without randomization; II-2, evidence from well designed cohort or case-control analytic studies, preferably from more than 1 center or research group; II-3, evidence from comparisons between times or places with or without the intervention (dramatic results in uncontrolled experiments could also be included here); and III, opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Assess Bleeding Risk

Patients should then be assessed for potential factors that may increase their risk of anticoagulant-related bleeding. **Table 2** outlines the recommendations relative to these factors on the decision whether to initiate anticoagulant therapy. If the patient has a potentially rectifiable absolute or relative contraindication to anticoagulant therapy, measures to alleviate this condition should be considered. For example, some older persons with AF may also have mild to moderate dementia. They may still be candidates for anticoagulant therapy. However, it would be difficult to initiate anticoagulant therapy in these persons if they were living alone and their compliance with warfarin therapy or their ability to remember to return for regular blood testing was not assured. To help ensure compliance, attempts could be made to enlist the help of family or friends, or a move to a supervised setting might be considered. Anticoagulant therapy could then be initiated with greater confidence. Another option is alternative therapies, such as cyclooxygenase-2 inhibitor–specific NSAIDs in patients who are taking conventional NSAIDs without cytoprotection. For persons taking cyclooxygenase-2 inhibitor–specific NSAIDs, the role of the addition of misoprostol or a proton-pump inhibitor in the prevention of GI tract bleeding requires further study.

Assess Patient Preferences

For patients who remain candidates for anticoagulant therapy after assessment of their bleeding risk, the recommendations of the 6th American College of Chest Physicians Conference on Antithrombotic Therapy for older persons with AF should be used as a guide to appropriate therapy.² These guidelines recommend anticoagu-

lant therapy for all patients with AF who are 75 and older unless a contraindication exists. For persons aged 65 to 74, anticoagulant agents are recommended unless their baseline stroke risk is low (4%-5% per year), in which case aspirin and, possibly, no therapy become viable therapeutic options. Finally, in discussion with individual patients, it is important that their preferences for therapy be determined. That is, the benefits of antithrombotic therapy (oral anticoagulant agents and aspirin) and the potential disadvantages (eg, the need for regular blood testing during warfarin therapy) should be discussed with them. This is important because studies⁷²⁻⁷⁴ have found that patients with AF with similar clinical profiles choose different stroke prevention therapies. Several methods have been developed to help elicit these preferences, although they may be difficult to perform in the usual clinical care setting. However, they highlight the need for clinicians to receive feedback from patients about how they personally weigh the advantages and disadvantages of warfarin and aspirin therapy.

COMMENT

Based on the literature review for this study, many of the purported patient-related barriers to anticoagulant therapy in older persons with AF probably should not influence the choice of stroke prophylaxis in these patients. For example, in the era of routine clinical *H pylori* testing and treatment of persons with non-NSAID–induced peptic ulcer bleeding, previous episodes of upper GI tract bleeding do not appear to increase the chance of anticoagulant-related bleeding. Furthermore, for many clinically accepted contraindications to anticoagulant therapy, such as alcohol abuse, there is conflicting evidence pertaining to their effect on warfarin-related bleeding. Decision making regarding the use of anticoagulant agents

in such persons continues to require clinical judgment. For other purported contraindications, such as the notion that there is an unacceptably high risk of anticoagulant-related bleeding in the very old (≥ 75 years), there is little supporting evidence.

Recognizing that an increased risk of bleeding is a major disadvantage of anticoagulant therapy and that older age may confer a slightly higher risk of developing anticoagulant-related bleeding complications, it must be remembered that of all age groups, patients older than 65 are also at the highest risk of stroke from AF. Therefore, as pointed out by Hart,⁷⁵ older persons with AF have the most to gain from treatment with anticoagulant agents but also potentially have the most to lose. Considering that multiple studies⁷⁶⁻⁷⁹ have shown that, among all age groups, older persons with AF are the least likely to receive anticoagulant therapy, it seems that many clinicians are overly concerned about the possible negative effects of anticoagulant therapy and tend to underemphasize its potential benefits.^{13,80} The results and recommendations of these studies and the present study may help place the advantages and disadvantages of anticoagulant therapy in this population in better perspective.

This study has addressed the bleeding-related barriers to anticoagulant therapy in older patients with AF. However, there are numerous physician-related barriers as well.⁸¹ For example, longitudinal follow-up by physicians and nurses of patients receiving chronic anticoagulant therapy can be disruptive to a busy office practice. There is frequent and regular need to communicate with laboratories regarding INR results and to speak with patients regarding changes in their anticoagulant dosage. Considering that in many jurisdictions these activities are also poorly remunerated, physicians may choose the path of most convenience and recommend aspirin therapy for many of their older patients with AF who are appropriate candidates for anticoagulant therapy.⁸² The access of these physicians to dedicated multidisciplinary anticoagulation clinics that are capable of taking over the day-to-day responsibility for management of anticoagulant therapy may represent a solution to this problem. Compared with management in primary care physicians' offices, these clinics have been shown to reduce the incidence of anticoagulant-related bleeding complications.⁸² Further study is needed to determine whether increased access to them will increase the percentage of patients with AF appropriately treated with anticoagulant agents. Other suspected physician barriers to the use of anticoagulant therapy include the general tendency of physicians to more easily accept an error of omission over an error of commission.⁸³⁻⁸⁶ In other words, physicians may believe that they are personally responsible when patients have anticoagulant-related bleeding episodes, in opposition to when patients with AF have strokes that could have been prevented with anticoagulant therapy.¹³ Further work is necessary to examine the influence of these physician-related barriers on the appropriate use of anticoagulant agents in older patients with AF.

In summary, the salient issue in selecting patients with AF for anticoagulation therapy is accurately estimating their stroke risk, with bleeding risk during anticoagulation being a lesser issue, relevant to only a few

patients. Therefore, physicians' fears of the risk of bleeding among older patients who are taking anticoagulant agents are often exaggerated and unfounded. Stroke risk stratification should drive the decision about use of anticoagulation in these patients. Based on the risks of stroke and bleeding, clinicians can use the approach outlined in this article to determine the appropriate use of warfarin therapy in older persons with AF.

Accepted for publication September 19, 2002.

We thank Robert G. Hart, MD, for his helpful comments. We also thank Leslie Ann Balliau, MD, Margaret Manville, MD, Frank Molnar, MD, and Pamela Thornton, MD, for independently assessing the treatment recommendations.

Corresponding author: Malcolm Man-Son-Hing, MD, Geriatric Assessment Unit, Ottawa Hospital, Civic Campus, 1053 Carling Ave, Ottawa, Ontario, Canada K1Y 4E9 (e-mail: mhing@ottawahospital.on.ca).

REFERENCES

1. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. *Arch Intern Med.* 1995; 155:469-473.
2. Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. *Chest.* 2001;119(suppl):194S-206S.
3. Gage BF, Waterman AD, Shannon W, Boechler M, Rich M, Radford MJ. Validation of clinical classification schemes for predicting stroke. *JAMA.* 2001;285: 2864-2870.
4. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med.* 1999; 131:492-501.
5. Atrial Fibrillation Investigators. Atrial fibrillation: risk factors for embolization and efficacy of antithrombotic therapy. *Arch Intern Med.* 1994;154:1449-1457.
6. Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation: analysis of pooled data from 3 randomized trials. *Arch Intern Med.* 1997; 157:1237-1240.
7. Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA.* 1995;274:1839-1845.
8. Lightowler S, McGuire A. Cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. *Stroke.* 1998; 29:1827-1832.
9. Gustafsson C, Asplund K, Britton M, Norrving B, Olsson B, Marke LA. Cost effectiveness of primary stroke prevention in atrial fibrillation: Swedish national perspective. *BMJ.* 1992;305:1457-1460.
10. Arnsten JH, Gelfand JM, Singer DE. Determinants of compliance with anticoagulation: a case-control study. *Am J Med.* 1997;103:11-17.
11. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. *Arch Intern Med.* 1993;153:1665-1670.
12. Lundstrom T, Ryden L. Hemorrhagic and thromboembolic complications in patients with atrial fibrillation on anticoagulant prophylaxis. *J Intern Med.* 1989; 225:137-142.
13. Beyth RJ, Antani MR, Covinsky KE, et al. Why isn't warfarin prescribed to patients with nonrheumatic atrial fibrillation? *J Gen Intern Med.* 1996;11:721-728.
14. Man-Son-Hing M, Laupacis A. Balancing the risks of stroke and gastrointestinal bleeding in older persons with atrial fibrillation. *Arch Intern Med.* 2002;162:541-550.
15. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med.* 1999;159:677-685.
16. Labenz J, Borsch G. Role of *Helicobacter pylori* eradication in the prevention of peptic ulcer bleeding relapse. *Digestion.* 1994;55:19-23.
17. Rokkas T, Karameris A, Mavrogeorgis A, Rallis E, Giannikos N. Eradication of *Helicobacter pylori* reduces the possibility of rebleeding in peptic ulcer disease. *Gastrointest Endosc.* 1995;41:1-4.
18. Garrigan K, McIntosh C, Fraser AG. Bleeding peptic ulcers: audit of eradication treatment for *H. pylori*. *N Z Med J.* 1999;112:178-180.
19. Hernandez-Diaz S, Garcia Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med.* 2000; 160:2093-2099.
20. Yeomans ND, Tulassay Z, Juhasz L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. *N Engl J Med.* 1998;338:719-726.

21. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. *Ann Intern Med.* 1995;123:241-249.
22. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA.* 1999;282:1929-1933.
23. Saloheimo P, Juvela S, Hillbom M. Use of aspirin, epistaxis, and untreated hypertension as risk factors for primary intracerebral hemorrhage in middle-aged and elderly people. *Stroke.* 2001;32:399-404.
24. Brott T, Thalinger K, Hertzberg V. Hypertension as a risk factor for spontaneous intracerebral hemorrhage. *Stroke.* 1986;17:1078-1083.
25. Qureshi AI, Tuhim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. *N Engl J Med.* 2001;344:1450-1460.
26. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med.* 1994;120:897-902.
27. Kase CS, Robinson RK, Stein RW, et al. Anticoagulant-related intracerebral hemorrhage. *Neurology.* 1985;35:943-948.
28. Mattle H, Kohler S, Huber P, Rohner M, Steinsiepe KF. Anticoagulation-related intracranial extracerebral haemorrhage. *J Neurol Neurosurg Psychiatry.* 1989;52:829-837.
29. Wintzen AR, de Jonge H, Loeliger EA, Bots GTA. The risk of intracerebral hemorrhage during oral anticoagulant treatment: a population study. *Ann Neurol.* 1984;16:553-558.
30. Dawson I, van Bockel JH, Ferrari MD, van der Meer FJ, Brand R, Terpstra JL. Ischemic and hemorrhagic stroke in patients on oral anticoagulants after reconstruction for chronic lower limb ischemia. *Stroke.* 1993;24:1655-1663.
31. Roos J, van Joost HE. The cause of bleeding during anticoagulant treatment. *Acta Med Scand.* 1965;178:129-131.
32. Stroke Prevention in Atrial Fibrillation Investigators. Bleeding during antithrombotic therapy in patients with atrial fibrillation. *Arch Intern Med.* 1996;156:409-416.
33. Wintzen AR, Tijssen JGP. Subdural hematoma and oral anticoagulant therapy. *Arch Neurol.* 1982;39:69-72.
34. Jones NR, Blumberg PC, North JB. Acute subdural hematomas: aetiology, pathology and outcome. *Aust N Z J Surg.* 1986;56:907-913.
35. Black DW. Subdural hematoma: a retrospective study of the "great neurological imitator." *Postgrad Med.* 1985;78:107-114.
36. Christiaens JL, Combelles G, Bousquet C, et al. Hémorragies intra-crâniennes et intra-rachidiennes chez des malades sous traitement anticoagulant: a propos de 33 cas. *Lille Med.* 1980;25:178-182.
37. Fihn SD, Callahan CM, Martin DC, McDonnell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin: the National Consortium of Anticoagulation Clinics. *Ann Intern Med.* 1996;124:970-979.
38. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT): Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet.* 1996;348:423-428.
39. van der Meer FJM, Posendaal FR, Vanderbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. *Arch Intern Med.* 1993;153:1557-1562.
40. Dahl T, Abildgaard U, Sandset PM. Long-term anticoagulant therapy in cerebrovascular disease: does bleeding outweigh the benefit? *J Intern Med.* 1995;237:323-329.
41. Launbjerg J, Egeblad H, Heaf J, Nielsen NH, Fugleholm AM, Ladefoged K. Bleeding complications to oral anticoagulant therapy: multivariate analysis of 1010 treatment years in 551 outpatients. *J Intern Med.* 1991;229:351-355.
42. White RH, McKittrick T, Takakuwa J, Callahan C, McDonnell M, Fihn S. Management and prognosis of life-threatening bleeding during warfarin therapy. *Arch Intern Med.* 1996;156:1197-1201.
43. Petty GW, Lennihan L, Mohr JP, et al. Complications of long-term anticoagulation. *Ann Neurol.* 1988;23:570-574.
44. Levine MN, Raskob G, Hirsh J. Hemorrhagic complications of long-term anticoagulant therapy. *Chest.* 1989;95(suppl):26S-36S.
45. Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. *Ann Neurol.* 1997;42:857-865.
46. European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med.* 1995;333:5-10.
47. European Atrial Fibrillation Trial Study Group. Secondary prevention on nonrheumatic atrial fibrillation after transient ischemic attack or minor stroke. *Lancet.* 1993;342:1255-1262.
48. McVay PA, Toy PTCY. Lack of increased bleeding after liver biopsy in patients with mild hemostatic abnormalities. *Am J Clin Pathol.* 1990;94:747-753.
49. McVay PA, Toy PTCY. Lack of increased bleeding after paracentesis and thoracentesis in patients with mild coagulation abnormalities. *Transfusion.* 1991;31:164-171.
50. Rintels PB, Kenney RM, Crowley JP. Therapeutic support of patients with thrombocytopenia. *Hematol Oncol Clin North Am.* 1994;8:1131-1157.
51. White RH, Beyth R, Zhou H, et al. Major bleeding after hospitalization for deep venous thrombosis. *Am J Med.* 1999;107:414-424.
52. Bridgen ML, Kay C, Le A, Graydon C, McLeod B. Audit of the frequency and clinical response to excessive oral anticoagulation in an out-patient population. *Am J Hematol.* 1998;59:22-27.
53. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med.* 1989;87:144-152.
54. Isaacs C, Paltiel O, Blake G, Beaudet M, Conochie L, Leclerc J. Age-associated risks of prophylactic anticoagulation in the setting of hip fracture. *Am J Med.* 1994;96:487-491.
55. McMahan DA, Smith DM, Carey MA, Zhou XH. Risk of major hemorrhage for outpatients treated with warfarin. *J Gen Intern Med.* 1998;13:311-316.
56. Pettiti D, Strom B, Melmon K. Duration of warfarin anticoagulation therapy and the probabilities of recurrent thromboembolism and hemorrhage. *Am J Med.* 1986;81:255-259.
57. Fihn SD, McDonnell M, Martin D, et al. for the Warfarin Optimized Outpatient Follow-up Study Group. Risk factors for complications of chronic anticoagulation: a multicenter study. *Ann Intern Med.* 1993;118:511-520.
58. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. *Chest.* 2001;119(suppl):108S-121S.
59. Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA.* 1998;279:657-662.
60. Man-Son-Hing M, Laupacis A, O'Connor AM, et al. Development of a decision aid for patients with atrial fibrillation who are considering antithrombotic therapy. *J Gen Intern Med.* 2000;15:723-730.
61. Hull R, Hirsh J, Jay R, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. *N Engl J Med.* 1982;307:1676-1681.
62. Turpie AG, Gunstensen J, Hirsh J, Nelson H, Gent M. Randomised comparison of two intensities of oral anticoagulant therapy after tissue heart valve replacement. *Lancet.* 1988;1:1242-1245.
63. Saour JN, Sieck JO, Mamo LA, et al. Trial of two different intensities of anticoagulation in patients with prosthetic heart valves. *N Engl J Med.* 1990;322:428-432.
64. Hylek EM. Oral anticoagulants: pharmacologic issues for use in the elderly. *Clin Geriatr Med.* 2001;17:1-13.
65. Hylek E, Go A, Chang Y, et al. Increasing age is not associated with poorer anticoagulation control in outpatients with nonvalvular atrial fibrillation [abstract]. *J Am Geriatr Soc.* 2000;48:S58.
66. Pettiti DB, Strom BL, Melmon KL. Prothrombin time ratio and other factors associated with bleeding in patients treated with warfarin. *J Clin Epidemiol.* 1989;42:759-764.
67. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II study. *Lancet.* 1994;343:687-691.
68. Beyth RJ, Landefeld CS. Are older patients at increased risk for major bleeding during anticoagulant therapy [abstract]? *Clin Res.* 1992;40:552A.
69. Gurwitz JH, Goldberg RJ, Holden A, Knapic N, Ansell J. Age-related risks of long-term oral anticoagulant therapy. *Arch Intern Med.* 1988;148:1733-1736.
70. Stroke Prevention in Atrial Fibrillation Investigators. Risk factors for thromboembolism during aspirin therapy in patients with atrial fibrillation. *J Stroke Cerebrovasc Dis.* 1995;5:147-157.
71. Canadian Task Force on Preventive Health Care. *History and Methods.* Ottawa, Ontario: Health Canada. Available at: <http://www.ctfphc.org>. Accessed October 29, 2001.
72. Man-Son-Hing M, Laupacis A, O'Connor AM, et al. Warfarin for atrial fibrillation: the patient's perspective. *Arch Intern Med.* 1996;156:1841-1848.
73. Gage BF, Cardinalli AB, Owens DK. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. *Stroke.* 1998;29:1083-1091.
74. Thomson RG, Parkin D, Eccles M, Sudlow M, Robinson A. Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. *Lancet.* 2000;355:956-962.
75. Hart RG. Anticoagulation therapy for patients with atrial fibrillation [letter]. *CMAJ.* 2000;163:956-957.
76. Stafford RS, Singer DE. National patterns of warfarin use in atrial fibrillation. *Arch Intern Med.* 1996;156:2537-2541.
77. Antani MR, Beyth RJ, Covinsky KE, et al. Failure to prescribe warfarin to patients with nonrheumatic atrial fibrillation. *J Gen Intern Med.* 1996;11:713-720.
78. Lawson F, McAlister F, Ackman M, Ikuta R, Montague T. The utilization of antithrombotic prophylaxis for atrial fibrillation in a geriatric rehabilitation hospital. *J Am Geriatr Soc.* 1996;44:708-711.
79. Albers GW, Yim JM, Belew KM, et al. Status of antithrombotic therapy for patients with atrial fibrillation in university hospitals. *Arch Intern Med.* 1996;156:2311-2316.
80. Sudlow M, Thomson R, Rodgers H, Livingstone S, Kenny RA. The effect of age and quality of life in doctors' decisions to anticoagulate patients with atrial fibrillation. *Age Ageing.* 1998;27:285-289.
81. Matchar DB, Samsa GP, Cohen SJ. Should we just let the anti-coagulation service do it? the conundrum of anticoagulation for atrial fibrillation. *J Gen Intern Med.* 1996;11:768-770.
82. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med.* 1998;158:1641-1647.
83. Tversky A, Kahneman D. Judgement under uncertainty: heuristics and biases. *Science.* 1974;185:1124-1131.
84. Eraker SA, Polister P. How decisions are reached: physician and patient. *Ann Intern Med.* 1982;97:262-268.
85. Asch DA, Baron J, Hershey JC, et al. Omission bias and pertussis vaccination. *Med Decis Making.* 1994;14:118-123.
86. Feinstein AR. The "chagrin factor" and qualitative decision analysis. *Arch Intern Med.* 1985;145:1257-1259.