Anticoagulation: Stroke Prevention in Patients with Atrial Fibrillation

Albert L. Waldo, MD

EPIDEMIOLOGY OF STROKE RISK

It is well recognized that during atrial fibrillation (AF), clots may form in the left atrium, which may embolize and cause ischemic stroke or systemic embolism. The presence of AF confers a fivefold increased risk for stroke.[1] Moreover, the prevalence of stroke in patients who have AF increases with age. The prevalence is less than 0.5% in patients younger than 60 years, but virtually doubles with each decade beginning with the seventh. Therefore, the prevalence of AF is 2% to 3% for patients in their 60s, 5% to 6% in their 70s, and 8% to 10% in their 80s.[1] The population-attributable risk also increases with age, so that it is 16.5% by the 70s and just more than 30%.by the 80s.[1] Thus, unsurprisingly, AF is the most common and important cause of stroke.

STROKE RISK STRATIFICATION SCHEMES FOR PATIENTS WHO HAVE ATRIAL FIBRILLATION

The risk for stroke varies among all patients who have AF. Based on a series of studies, the widely recognized risk factors are prior stroke or transient ischemic attack (TIA), hypertension, age of 75 years or older, heart failure and poor left ventricular function, and diabetes.[2,3] Other recognized stroke risk factors include mechanical prosthetic valve, mitral stenosis, coronary artery disease, age of 65 to 74 years, thyrotoxicosis, and female gender.[4] All of these factors are important when considering indications for oral anticoagulation. As incorporated into the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2006 revised Guidelines for the Management of Patients with Atrial Fibrillation, not all stroke risk factors have the same degree of association with stroke in patients who have AF.[4]

Several stroke risk stratification schemes for patients who have AF are available. One that has gained great favor is the CHADS2 scheme.[5] Based on analysis of 1773 patients in the National Registry of Atrial Fibrillation, it uses most of the accepted stroke risk factors to assess individual patient risk. The *C* stands for recent congestive heart failure, the *H* for hypertension, the *A* for age 75 or older, the *D* for diabetes, and the *S* for prior stroke or TIA. Each category is assigned one point except stroke or TIA, which gets two because of its high association with subsequent stroke. The adjusted stroke rate per 100 patient years increases as the CHADS2 score increases (**Fig. 1**).

The Framingham risk score[6] uses five steps to predict the 5-year risk for stroke in patients who have AF (**Fig. 2**). The steps consider age, gender, systolic blood pressure, diabetes, and prior stroke or TIA, and assign points depending on these factors. The points from steps 1 through 5 are added, and then the predicted 5-year stroke risk for each individual in the absence of anticoagulation therapy is determined from a table. This strategy may help in weighing available therapeutic options and even enable patients to understand the need for anticoagulation therapy.

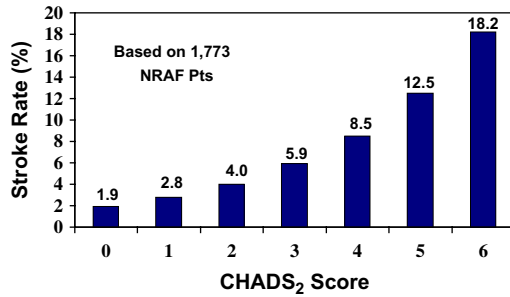| Risk Factor	Points
C Congestive heart failure (recent)	1
H Hypertension	1
A Age ≥ 75 yrs	1
D Diabetes	1
S_2 Prior stroke/TIA	2

Fig. 1. Key AF stroke risk factors: $CHADS2$ risk stratification scheme. NRAF, National Registry of Atrial Fibrillation. (*Data from* Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from a national registry of atrial fibrillation. JAMA 2001;285:2864–70.)

PROPHYLAXIS AGAINST STROKE
Warfarin Therapy

Many clinical trials have shown warfarin's remarkable efficacy in reducing stroke risk in patients who have AF. As shown overwhelmingly almost 15 years ago in a meta-analysis[3] of five randomized, controlled clinical trials comparing warfarin and placebo in patients who had AF (Copenhagen Atrial Fibrillation Aspirin and Anticoagulation [AFASAK],[7] Stroke Prevention in Atrial Fibrillation [SPAF],[8] Boston Area Anticoagulation Trial for Atrial Fibrillation [BAATAF],[9] Canadian Atrial Fibrillation Anticoagulation [CAFA],[10] and Stroke Prevention in Nonrheumatic Atrial Fibrillation [SPINAF],)[11] the intention-to-treat analysis showed that patients taking warfarin had a 68% risk reduction in stroke compared with those taking placebo ($P < .001$).[3]

An on-treatment analysis of these same trials showed an 83% risk reduction for stroke in patients taking warfarin compared with placebo.[12]

These and subsequent data established warfarin's therapeutic range as an international normalized ratio (INR) between 2 and 3, with a target INR of 2.5 to provide efficacy and safety.

Despite warfarin's well-demonstrated efficacy as prophylaxis against stroke in patients who have AF, many problems impact its use. These disadvantages include a narrow therapeutic range (INR 2–3), an unpredictable and patient-specific dose response, delayed onset and offset of action, need for anticoagulation monitoring, slow reversibility when that may be necessary, and many drug–drug and drug–food interactions that affect INR levels.[13] Drug interactions with warfarin are common and include virtually all anti-inflammatory drugs, most antibiotics, many diuretics, phenytoin, prednisone, thyroid hormone replacement, tamoxifen, alcohol, and statins.[13] Many foods also interact, including those high in vitamin K (eg, green, leafy vegetables; kiwi), high-dose vitamin C, vitamin E, cranberries, and licorice.[13]
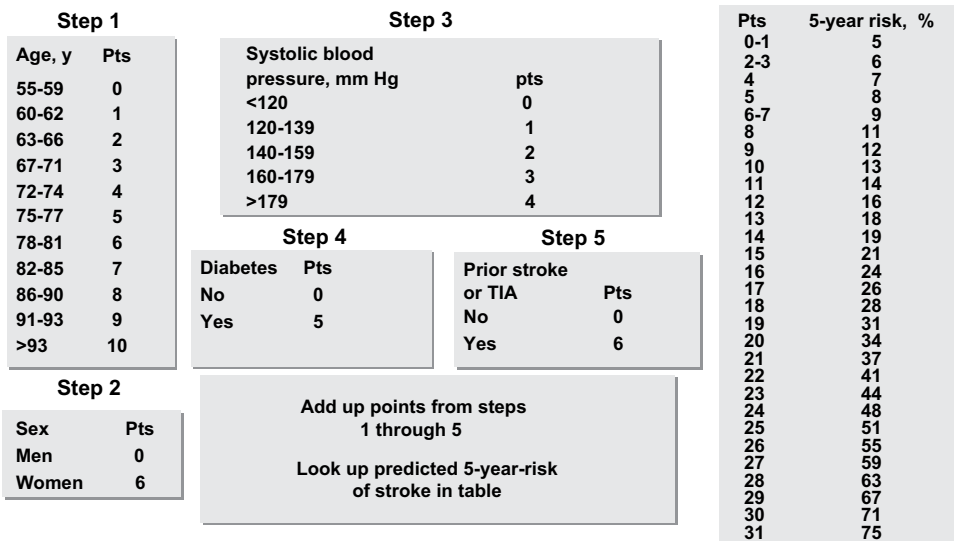
Step 1

Age, y	Pts
55-59	0
60-62	1
63-66	2
67-71	3
72-74	4
75-77	5
78-81	6
82-85	7
86-90	8
91-93	9
>93	10

Step 2

Sex	Pts
Men	0
Women	6

Step 3

Systolic blood pressure, mm Hg	pts
<120	0
120-139	1
140-159	2
160-179	3
>179	4

Step 4

Diabetes	Pts
No	0
Yes	5

Step 5

Prior stroke or TIA	Pts
No	0
Yes	6

Add up points from steps 1 through 5

Look up predicted 5-year-risk of stroke in table

Pts	5-year risk, %
0-1	5
2-3	6
4	7
5	8
6-7	9
8	11
9	12
10	13
11	14
12	16
13	18
14	19
15	21
16	24
17	26
18	28
19	31
20	34
21	37
22	41
23	44
24	48
25	51
26	55
27	59
28	63
29	67
30	71
31	75

Fig. 2. Framingham risk score for predicting the 5-year risk of stroke in patients who have AF. (*Data from* Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA 2003;290:1049–105).

Furthermore, warfarin has a narrow therapeutic range, because once the INR falls below 2, the odds ratio for stroke rises steeply (eg, an INR of 1.7 doubles this risk) (**Fig. 3**).[14] When the INR rises to more than 3, it does not enhance the therapeutic efficacy, but increases the risk for bleeding, with major hemorrhage and intracranial hemorrhage the two greatest concerns. An INR up to 3.5 (target 3.0) is acceptable and indicated for patients who have a mechanical heart valve. The incidence of intracranial hemorrhage is flat,[15,16] varying between 0.3 and 0.6 per 100 person years when the INR is between 1.5 and approximately 3.5 (see **Fig. 3**), and is also remarkably flat until patient age is 80 years or older. No difference is seen in occurrence of intracerebral hemorrhage or subdural hematoma.[16] These data help to show the therapeutic target and range for the INR.

In view of the recognized difficulties in administrating warfarin, the U. S. Food and Drug Administration approved safety labeling revisions to advise about the need for individualization of warfarin therapy to minimize the risk for bleeding.[13] The most serious risks associated with anticoagulant therapy with warfarin are hemorrhage in any tissue or organ and, less frequently (incidence <0.1%), necrosis or gangrene of skin or other tissues. The risk for bleeding is highest during treatment initiation and with higher doses. Risk factors include a high intensity of anticoagulation (INR ≥ 4), age 65 years or older, high variability of INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs, and long duration of warfarin therapy.

This safety relabeling appropriately emphasizes the need to individualize treatment with warfarin because of a low therapeutic index and potential effects from interaction with other drugs or foods, especially dietary vitamin K intake. Regular monitoring of the INR, usually at least monthly, is recommended for all patients. Those at high risk for bleeding may benefit from more frequent monitoring, careful dose adjustments to achieve the desired INR, and, when possible, shorter duration of therapy. To minimize the risk for bleeding, patients should be advised to avoid initiating or discontinuing other medications, including salicylates, and should be wary of other over-the-counter medications and herbal products. Maintaining a balanced diet with a consistent amount of vitamin K is advised. Drastic changes in diet (eg, eating large amounts of green leafy vegetables) and consumption of cranberry juice or its products should be avoided.

Despite the recognized indications for warfarin use and its clear efficacy in stroke prevention, warfarin therapy remains underused.[17] Most studies indicate use between 40% and 60% in patients who have AF and risk factors for stroke. Additionally, although the risk for stroke notably increases with increasing age, the use of warfarin decreases as patients get older,[17] with elderly persons using warfarin the least. In this latter group, a principle reason seems to be fear of an intracranial hemorrhage. Although whether to use warfarin must be decided on a case-by-case basis, the risks for potential intracranial hemorrhage or major bleeding usually are outweighed significantly by the risks for stroke or systemic embolus, so that often warfarin therapy is warranted.[18,19]

Aspirin

Aspirin as prophylaxis against stroke is controversial in patients who have AF and stroke risks.
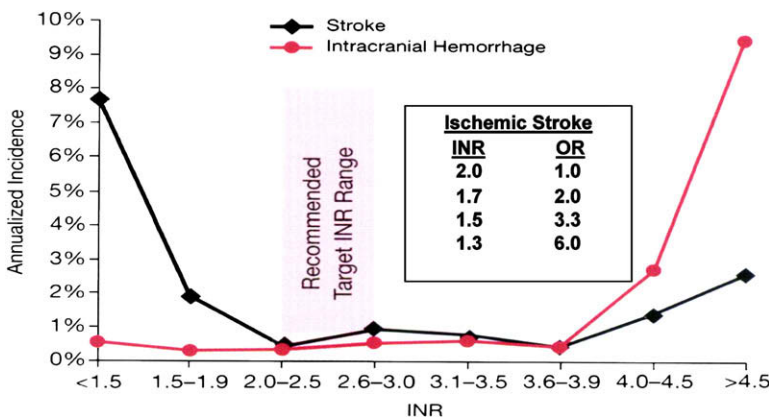
Fig. 3. Annualized incidence of stroke or intracranial hemorrhage according to international normalized ratio (INR). Also included is the odds ratio (OR) for ischemic stroke in patients who have AF based on their INR. (*Data from* Hylek E, Skates S, Sheehan M, et al. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med 1996;335:540–6; and Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019–26.)

Meta-analysis of studies comparing aspirin with placebo suggest a relative risk reduction of approximately 22% with use of aspirin.[20] This is driven in large part, however, by data from one clinical trial, the SPAF I study (**Fig. 4**). Only these data indicate that aspirin is significantly better than placebo, but these results should be examined closely (see **Fig. 4**).[21] SPAF I was a National Institutes of Health–sponsored trial that randomized patients who had AF to treatment with warfarin, aspirin, or placebo (group I) or, for those who had a relative or absolute contraindication to warfarin, to aspirin versus placebo (group II). In group I, of 206 patients in the aspirin arm, only one event occurred, whereas 18 events occurred among 211 patients in the placebo arm, resulting in a relative risk reduction of 94% for aspirin ($P < .001$). No other data have confirmed these results, suggesting that they are outliers. Moreover, in group II, 25 events occurred among 346 patients in the aspirin arm and 26 events among 357 patients in the placebo arm, giving aspirin a relative risk reduction of 8% ($P = .75$). The aspirin versus placebo data from groups I and II were pooled, resulting in a 42% ($P = .02$) relative risk reduction for aspirin. The confidence intervals of the pooled data are wide, however, because of the disparate nature of the data reported. Thus, this relative risk reduction should be considered unreliable.

Other data suggest that aspirin is less effective than desirable. Unlike warfarin, aspirin was never shown to affect mortality in patients who have AF.[22] In addition, the SPAF III trial[23] evaluated the benefit of an adjusted dose of warfarin (INR, 2–3; target 2.5) versus low-intensity, fixed-dose warfarin (INR, 1.2–1.5) plus aspirin in patients who had AF at high risk for stroke (ie, patients who had one or more of the following risk factors: female gender and age

of 75 years; impaired left ventricular function; systolic blood pressure greater than 160 mm Hg; or prior thromboembolism).[24] The investigators reasoned that warfarin was more effective than aspirin as prophylaxis against stroke, but there was concern about excess and serious bleeding in patients receiving warfarin. The hope was that combining aspirin (324 mg daily) with a fixed but low dose of warfarin to achieve an INR between 1.2 and 1.5 would provide effective stroke prevention but avoid the bleeding risks associated with adjusted-dose warfarin administered to achieve an INR between 2 and 3.

However, the trial was stopped early (after a mean follow-up of 1.1 years) because the event rate in patients undergoing combination therapy was 7.9% per year versus an event rate on adjusted-dose warfarin of 1.9% per year ($P = .001$) (**Fig. 5**).[23] Moreover, no significant difference was seen in major bleeding and intracranial hemorrhage rates between the groups. Slightly more major bleeding and intracranial hemorrhage was seen in the group receiving aspirin plus fixed low-dose warfarin compared with the group receiving adjusted-dose warfarin (see **Fig. 5**). Furthermore, the annual event rate of stroke began to increase in the adjusted-dose warfarin group as soon as the INR fell below 2; whereas the incidence of stroke decreased as the INR approached 2 in the group receiving combination aspirin and fixed low-dose warfarin (**Fig. 6**). Additionally, SPAF III had a low–stroke-risk patient cohort (patients who had AF who had no high risk factors for stroke) in a nonrandomized, aspirin-only arm of this trial. In these patients, just a history of hypertension conferred a 3.6% risk for stroke or systemic embolism per year.[24]

Additional data indicate the problems with aspirin therapy compared with warfarin therapy. Hylek and colleagues[14] studied a cohort of 13,559

Aspirin Eligible AF Patients – SPAF I Trial
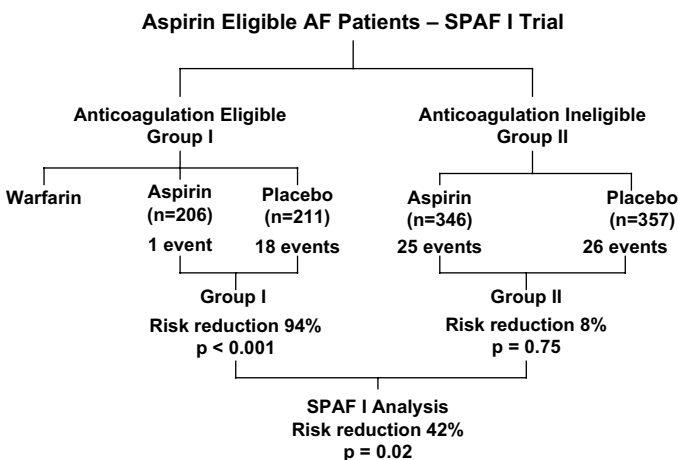
Fig. 4. Analysis of the data from the SPAF I trial in patients taking aspirin compared with placebo. (*Data from* The SPAF Investigators. A differential effect of aspirin on prevention of stroke in atrial fibrillation. J Stroke Cerebrovasc Dis 1993;3:181–8.)
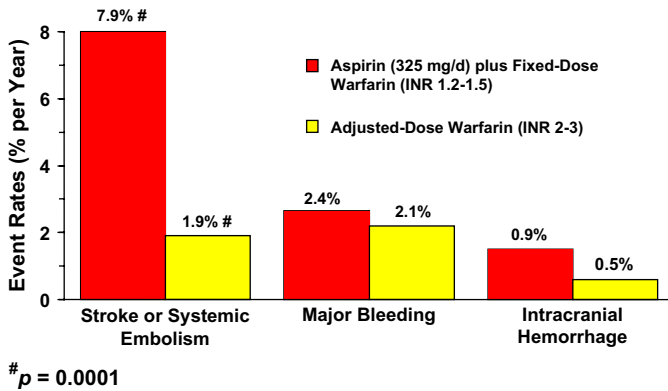
Fig. 5. Analysis of the SPAF III data in the high-risk patient cohort. (*Data from* Israel CW, Gronefeld G, Ehrlich JR, et al. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. J Am Coll Cardiol 2004;43:47–52.)

patients who had nonvalvular AF who experienced 596 ischemic strokes. Among these patients, 32% were on warfarin, 27% were undergoing aspirin therapy, and 42% were on neither warfarin nor aspirin therapy. The investigators compared the severity of neurologic deficit at discharge and the early and 30-day mortality rates in patients who had a stroke while receiving warfarin (with an INR $\geq$ 2 or < 2), aspirin, or no antithrombotic therapy. Patients taking aspirin or warfarin but who had an INR of less than 2 had a 2.6- to 3-fold increase in the severity of the stroke, including early (in-hospital) fatality or stroke resulting in total dependence, compared with patients who had an INR of greater than or equal to 2. Similarly, the 30-day mortality rate was approximately 2.5 times greater in patients taking aspirin or who had an INR less than 2 if taking warfarin compared with those

who had an INR greater than or equal to 2. In short, these data showed that warfarin with an INR greater than or equal to 2 not only reduced the frequency of ischemic stroke but also reduced the severity and risk for death from stroke compared with aspirin.

Data from the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study,[25] a trial of warfarin versus aspirin therapy for stroke prevention in an elderly (age $\geq$ 75 years, mean 82) community with AF, add still more to the limits of the effectiveness of aspirin. In this elderly patient population, for the combined primary end point of fatal or nonfatal disabling stroke or significant arterial embolism, patients taking warfarin experienced significantly fewer events than patients taking aspirin ($P = .007$; hazard ratio, 0.48). Not only did the data show warfarin was significantly better than aspirin in stroke prevention ($P = .003$; relative risk reduction, 46%) and disabling nonfatal strokes ($P = .005$; relative risk reduction, 33%), but also no difference was seen in the incidence of hemorrhagic stroke ($P = .83$) or subdural hemorrhage ($P = .65$) between the groups. In the absence of contraindications, these data clearly support the use of warfarin over aspirin for people older than 75 years who have AF.

The meta-analysis performed in 2002 (perhaps a bit out of date) by van Walraven and colleagues[26] provides useful way to think about risks versus benefits of prophylaxis with warfarin or aspirin. Their meta-analysis concludes that treating 1000 patients who have AF for 1 year with warfarin instead of aspirin would prevent 23 ischemic strokes but cause nine additional major bleeds, including two hemorrhagic strokes. Thus, in patients who have AF and stroke risk factors, the risk for stroke or systemic embolism is significant. However, the risks for bleeding also must be taken into account, although in most patients, the risk for stroke outweighs the risk for bleeding. Therefore,
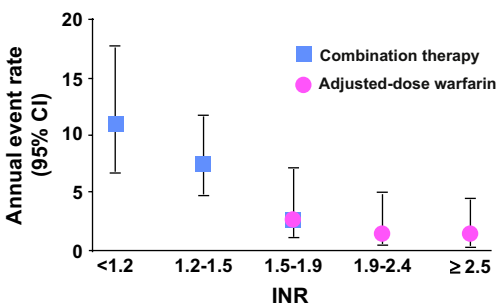

Fig. 6. SPAF III relative risk for stroke or systemic embolism in adjusted-dose warfarin and combination therapy cohorts. Event rates for ischemic stroke for systemic embolism based on the INR in SPAF III patients in the combination therapy (*square*) and adjusted-dose warfarin therapy (*circle*) groups. (*Data from* The SPAF Investigators. Adjusted-dose warfarin versus low-intensity, fixed dose warfarin plus aspirin for high-risk patients with atria fibrillation: Stroke Prevention in Atrial Fibrillation III randomized clinical trial. Lancet 1996;348:633–8.)

warfarin therapy should be administered in patients who have AF and are at high risk for stroke.

For patients who have AF and are not at high risk for stroke or systemic embolism, administration of warfarin seems to make the most sense unless it is contraindicated, although the Guidelines for the Management of Atrial Fibrillation offer aspirin or warfarin as options for therapy.[4] In sum, in patients at risk for stroke caused by AF, anticoagulation with warfarin (INR, 2–3; target, 2.5) reduces stroke rate and mortality, and also reduces morbidity associated with stroke if the latter occurs. Aspirin has considerably less, if not just minimal, effect on stroke rate and severity, and no demonstrated effect on mortality associated with stroke.

Emerging New Anticoagulants

The problems associated with the use of warfarin and the limited efficacy of aspirin in stroke prevention in patients who have AF highlight the unmet need for new, safe, and effective oral anticoagulants. Several promising agents are under active clinical study,[27] including dabigatran, a direct thrombin inhibitor (the RE-LY trial[27]); apixaban, a factor Xa inhibitor (the ARISTOTLE trial[27]); and rivaroxaban (the ROCKET-AF trial[27]), also a factor Xa inhibitor. These three trials are ongoing, and, in fact, the RE-LY trial stopped recruiting subjects in December, 2007. Therefore, whether these agents, which do not require anticoagulation monitoring and have little-to-no interaction with other drugs and food, will earn a place in the therapeutic armamentarium will be known in the very near future.

AMERICAN HEART ASSOCIATION/AMERICAN COLLEGE OF CARDIOLOGY/EUROPEAN SOCIETY OF CARDIOLOGY 2006 GUIDELINES ON RISK FACTORS FOR STROKE AND STROKE PREVENTION IN ATRIAL FIBRILLATION

The ACC/AHA/ESC 2006 revised Guidelines for the Management of Patients with Atrial Fibrillation[4] have divided risk factors for stroke into three groups (**Table 1**). High-risk factors include prior stroke, TIA, or thromboembolism; mitral stenosis; or presence of a prosthetic mechanical heart valve. Moderate risk factors include age older than 75 years, hypertension, heart failure, left ventricular ejection fraction less than or equal to 0.35, or diabetes mellitus. A third category might be called low risk, but is formally labeled less-validated or weaker risk factors, including female gender, age 65 to 74 years, coronary artery disease, and thyrotoxicosis.

In the presence of these risk factors, various recommendations for antithrombotic therapy have been made (see **Table 1**).[4] For patients who have any high risk factor for stroke, oral anticoagulation with warfarin therapy (range 2–3; target 2.5) is recommended. Similarly, oral anticoagulation with warfarin is recommended for patients who have two or more moderate stroke risk factors, whereas aspirin (81 or 324 mg) or oral anticoagulation with warfarin is recommended for patients who have one moderate risk factor. Aspirin (81 or 324 mg) or oral anticoagulation is recommended for patients who have less validated or weaker risk factors. For patients younger than 60 years, aspirin (81 or 324 mg) or no therapy is recommended. For patients who have no risk factors who are 60 to 65 years of age, aspirin (81 or 324 mg) or oral anticoagulation with warfarin is recommended. The indications for antithrombotic therapy are no different for persistent, permanent, or paroxysmal AF.

OTHER CONSIDERATIONS

Although these guidelines were designed carefully, some concerns exist. Data supporting the use of aspirin in patients who have stroke risk factors are wanting. The guidelines suggest that in patients older than 75 years who have risk factors for stroke but no history of stroke, and for whom no concern for bleeding exists, administering warfarin to achieve an INR of 1.6 to 2.5 with a target of 2 should be considered.[4] As the data reported by Hylek and colleagues[15] show, lowering the INR below 2 does not decrease the incidence of intracranial hemorrhage. However, it reduces the efficacy of warfarin therapy, causing that the odds ratio for stroke to increase dramatically (see **Fig. 3**). Thus, this IIc recommendation of the guidelines is questionable.

Managing anticoagulation interruptions is important. In general, the average weekly risk for stroke in the absence of oral anticoagulation is low but not zero. The highest risk is believed to be in patients who have mechanical heart valves or history of stroke.[4] In patients for whom the oral anticoagulation must be stopped for a procedure, bridging the interruption with unfractionated heparin or low molecular weight heparin therapy is recommended.[4] Thus, heparin or low molecular weight heparin therapy would be administered in lieu of warfarin through the day before the procedure, and then stopped. Warfarin or bridging with heparin usually is reinstated at a safe time after the procedure.

CARDIOVERSION

The question of adequate anticoagulation to prevent stroke in association with cardioversion has been standardized for a while, and has not changed with the 2006 revised ACC/AHA/ESC

Table 1
American Heart Association/American College of Cardiology/European Society of Cardiology 2006 revised guidelines for antithrombotic therapy based on stroke risk

Less Validated or Weaker Risk Factors	Moderate Risk Factors	High Risk Factors
Rx: ASA or OAC	Rx: 1 risk factor—ASA or OAC; ≥2 risk factors—OAC	Rx: OAC
Female gender Age 65–74 y Coronary artery disease Thyrotoxicosis	Age > 75 y Hypertension Heart failure LVEF ≤ 0.35 Diabetes mellitus	Prior stroke, TIA, or embolism Mitral stenosis Mechanical heart valve

Abbreviations: ASA, aspirin; LVEF, left ventricular ejection fraction; OAC, oral anticoagulation with warfarin; RF, stroke risk factor; Rx, therapy.
Data from Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to revise the 2001 guidelines for the management of patients with atrial fibrillation). J Am Coll Cardiol 2006;48:854–906.

guidelines (**Box 1**).[4] It is based on data and consensus. If AF is known to have been present for fewer than 48 hours, cardioversion may proceed without any anticoagulation. If AF has been present 48 hours or more, however, cardioversion raises the risk for embolism, with a 1% to 5% risk for emboli occurring within hours to weeks after cardioversion in the absence of anticoagulation. However, anticoagulation well before and after cardioversion greatly reduces this risk. Therefore, if AF has been present for two or more days or for an unknown period, the guidelines state that the INR should be between 2 and 3 for 3 weeks consecutively before cardioversion, and for at least 4 weeks after restoring and maintaining normal sinus rhythm.

If AF is present for two or more days in the absence of warfarin therapy with an INR in the therapeutic range, and if the clinician wants to perform a cardioversion, two options are available. One option is to perform a transesophageal echocardiogram in the presence of therapeutic heparin administration. If no thrombus is present, anticoagulation with heparin (unfractionated or low molecular weight) is continued through the cardioversion and as a bridge to achieving a therapeutic INR on warfarin, when the heparin is stopped. The warfarin is continued, maintaining an INR in the therapeutic range for at least 1 month after the successful cardioversion. If chronic warfarin therapy is indicated, it is continued. If it is not indicated, the warfarin is stopped. If a thrombus is present at precardioversion transesophageal echocardiography, however, anticoagulation with an INR between 2 and 3 for 3 days consecutively is recommended, followed by reevaluation. The second option is simply to provide oral anticoagulation with warfarin, and, after achieving an INR in

the therapeutic range for 3 weeks consecutively, then perform the cardioversion. Again, if long-term warfarin therapy is not indicated, it may be stopped after 1 month; otherwise, it is continued long-term. The ACUTE study[28] shows that the two approaches (transesophageal echocardiography with heparin before cardioversion or 3 consecutive weeks of an INR in the therapeutic range on warfarin) have no important difference in terms of morbidity and mortality.

Risk factors for stroke in AF do not apply to these rules. Thus, if patients have no risk factor for stroke and ordinarily would not need warfarin long-term, patients still should be anticoagulated before cardioversion if AF has been present for 48 or more hours or an unknown duration. The main reason is that an approximately 25% incidence of atrial stunning (absence of atrial contraction) exists after cardioversion for patients who have had AF for 48 or more hours.[29] The stunning may last up to 1 month, although most often it lasts only for hours or days after sinus rhythm is restored.[29] During this period of stunning is when the milieu that predisposes to left atrial clots is believed to still be present. Thus, clots may form in the left atrium during sinus rhythm. For patients who do not have a need for long-term anticoagulation, ordinarily the anticoagulation would be stopped after 1 month of therapy.

ISSUES IN LONG-TERM USE OF ORAL ANTICOAGULATION

What about continuation of warfarin therapy for patients who have AF and risk factors for stroke who achieve and seem to maintain sinus rhythm? Data from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM)[30,31] and

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Box 1

Elective cardioversion of atrial fibrillation anticoagulation: standards for use of anticoagulation in connection with cardioversion of atrial fibrillation

Cardioversion seems to increase risk for embolism

Anticoagulation well before and after greatly reduces risk

For use of anticoagulation, risk factors for stroke in AF do not apply

Standard guidelines for electrical or drug cardioversion

INR 2 to 3 for weeks before cardioversion and INR 2 to 3 for 4 weeks after normal sinus rhythm (continue warfarin beyond 4 weeks if stroke risk factors present)

If AF less than 2 days' duration, may proceed without AC

If transesophageal echocardiography performed and no thrombus; anticoagulation just before and 4 weeks after cardioversion

Thrombus present; anticoagulation with INR 2 to 3 for 3 weeks and reevaluate

Data from Fuster V, Ryden LE, Cannom DS, and colleagues ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to revise the 2001 guidelines for the management of patients with atrial fibrillation). J Am Coll Cardiol 2006;48:854–906.

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sinus rhythm and maintained it for at least 1 month, warfarin therapy could be stopped. This was worrisome because of the known tendency for AF to recur, but was requested by the study sites because they believed it would have a negative impact on patient recruitment to the study. The result was that patients in the rhythm control arm, initially more than 90% of patients took warfarin in the first 4 months after randomization. But by the end of year 1, this dropped to just under 80%, and by years 2 to 5, only approximately 70% were taking warfarin in the rhythm control arm. In the rate control arm, in which failure to use warfarin was a protocol violation, more than 90% of patients were taking warfarin through year 4, although by year 5, only approximately 85% were taking warfarin. Furthermore, throughout the AFFIRM study's 3.5-year average follow-up, only 84% of the rate control group and 52% of the rhythm control group remained continuously on warfarin. At the end of the AFFIRM trial, when the relationships among ischemic stroke, INR, and the presence of AF in the rate-versus-rhythm–control arms were examined (**Table 2**), the incidence of ischemic stroke was not significantly different between the arms ($P = .79$). However, 57% of the patients in the rhythm control arm who had a stroke were not taking warfarin. Although documented only partly in this trial, these patients probably experienced recurrence of AF, and much of it was likely asymptomatic.[33,34] Another 22% of patients who had a stroke in the rhythm control arm had an INR of less than 2, again emphasizing the importance of maintaining the INR in the therapeutic range. Additionally, in the rate control arm, 33% of patients who had a stroke were not taking warfarin, which was a protocol violation, emphasizing the difficulty of keeping patients on warfarin therapy even though its use is clearly indicated. Moreover, 36% of patients who had a stroke in the rate control arm also had an INR of less than 2, again emphasizing the importance of maintaining the INR

the Comparison of Rate Control and Rhythm Control in Patients with Recurrent Persistent Atrial Fibrillation (RACE)[32] trials are most instructive in this regard. In the AFFIRM trial, if a patient achieved

Table 2
The relationship between ischemic stroke, international normalization ratio, and presence or absence of atrial fibrillation

	Rate Control, n (%)	Rhythm Control, n (%)
Ischemic stroke	77 (5.5)[a]	80 (7.1)[a]
INR ≥ 2	23 (31)	16 (21)
INR < 2	27 (36)	17 (22)
Not taking warfarin	25 (33)	44 (57)
AF at time of event	42 (69)	25 (37)

[a] Event rates derived from Kaplan-Meier analysis ($P = .79$).
  Data from Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1825–33.

in the therapeutic range. Similar data were reported in the RACE trial.[31]

In patients who have AF, an estimated 10% to 30% of all AF cases are totally asymptomatic and up to 70% of patients who have symptomatic AF are believed to also have symptomatic episodes.[33] The risk for stroke in symptomatic and asymptomatic AF is similar,[4] and therefore asymptomatic AF requires not only ventricular rate control but also adherence to anticoagulation guidelines.

In addition, Israel and colleagues[34] examined the incidence of asymptomatic AF in patients who had a history of AF and also had an implanted pacemaker with excellent stored memory capacity and the ability to detect atrial arrhythmias. In 38% of patients who experienced AF recurrences, the AF was asymptomatic and lasted more than 48 hours, and 16% of them did so even after documentation of freedom from AF for 3 months. The implication is that success rates of maintaining continuous sinus rhythm in patients who have a history of AF often are grossly overestimated. And for patients who have AF and risk factors for stroke, the data suggest they should undergo warfarin therapy indefinitely, even when sinus rhythm seems to have been restored and maintained.

LONG-TERM ANTICOAGULATION AFTER RADIOFREQUENCY ABLATION OF ATRIAL FIBRILLATION

What should be done about long-term anticoagulation for patients who undergo apparently successful ablation to cure AF has yet to be determined. The hope is that these patients truly would be cured, so that the need for anticoagulation to prevent stroke resulting from AF is no longer present. These patients have an uncertain but real incidence of asymptomatic AF recurrence, however; both early and late after the ablation.[35] A difficulty in assessing long-term warfarin need in these patients is the absence of long-term data to give perspective, not only on the incidence of recurrence of AF beyond the 2- to 3-month "blanking period," when AF recurrence may not indicate failure of the procedure, but also on the incidence of stroke in the absence of anticoagulation therapy, especially in patients who have risk factors for stroke. In this sense, whether enough data exist even to reach an informed consensus must be considered.

For patients who do not have stroke risk factors (which is currently probably most of those who undergo apparently successful ablation of AF), consensus exists that after the blanking period,

further anticoagulation with warfarin is not necessary.[36–38] What should be done, then, for patients who have stroke risk factors? Data from small studies suggest that the stroke incidence is low, but the incidence of AF recurrence, manifest and asymptomatic, is uncertain. Moreover, data indicate a late AF recurrence (beyond the first year postablation) of at least 5%.[39,40] In addition, data suggest that not only does AF recurrence indicate the need for warfarin therapy in patients who have stroke risks, but also, as a consequence of radiofrequency ablation to cure AF, some patients experience up to a 30% reduction of left atrial transport function. The latter may predispose to thromboembolic events despite the presence of sinus rhythm.[40]

Because of these considerations and the absence of long-term, randomized, controlled trial data, the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[37] generally does not recommend discontinuation of warfarin therapy postablation in patients who have a CHADS2 score of 2 or more. It also recommends warfarin for all patients for at least 2 months after an AF ablation procedure. Whether to use warfarin for more than 2 months after the ablation should be decided based on patient risk factors for stroke. The Venice Chart International Consensus Document on Atrial Fibrillation[38] makes similar recommendations; the only real difference is that they recommend warfarin be given for at least 3 to 6 months after the ablation procedure.

OVERVIEW AFTER RADIOFREQUENCY ABLATION OF ATRIAL FIBRILLATION

The following is the author's considered overview for patients who have risk factors for stroke.

(1) For patients who require antiarrhythmic drug therapy after radiofrequency ablation to suppress AF recurrence (ie, despite radiofrequency ablation, cure has not been obtained, but successful therapy seemingly is obtained with the addition of antiarrhythmic drug therapy that was not successful before the ablation), warfarin therapy to maintain an INR in the therapeutic range should be continued long-term.

(2) For patients in whom no clinically manifest episodes of AF have been documented 2 months after ostensibly successful radiofrequency ablation to cure AF, warfarin therapy should be maintained for a minimum of 1 year, when

continued use of warfarin therapy should be reconsidered.

(3) For patients who have any documented recurrence of AF after the blanking period, warfarin therapy should be maintained for at least 1 year and then reconsidered.

(4) If asymptomatic AF does occur, warfarin therapy should be maintained long-term.

(5) A recommendation concerning continuation of warfarin therapy beyond 1 year postablation in patients who have stroke risks must be couched in uncertainties and considered on an individual basis. If no apparent AF recurrence has occurred, termination of warfarin therapy may be acceptable, with the understanding that the chance for late recurrence of AF, although likely to be low, is present, with the attendant risks. If patients experience AF recurrence, continued long-term warfarin therapy is recommended.

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