ASHP Therapeutic Position Statement on Antithrombotic Therapy in Chronic Atrial Fibrillation

Statement of Position

ASHP supports the routine use of antithrombotic therapy (warfarin or aspirin) for stroke prevention in patients with chronic atrial fibrillation (AF). Antithrombotic therapy given to patients with AF for primary prevention (before the first stroke or episode of systemic embolism) or as a secondary intervention (after stroke or systemic embolism has occurred) unequivocally reduces the risk of stroke. Warfarin is more effective than aspirin but carries a higher risk of bleeding and requires regular medical monitoring.

ASHP encourages the use of warfarin, if it can be administered safely, in all patients with chronic AF who are younger than 65 years and have clinical risk factors for stroke (Table 1) or who are older than 65. However, ASHP recognizes that, for patients who are ages 65 to 75 years and without clinical risk factors, either warfarin or aspirin may be an option, depending on individual patient circumstances. Aspirin may be an appropriate choice for AF patients younger than 65 with no risk factors and for any patient with AF who is not a candidate for warfarin therapy. There is no evidence that the combination of warfarin and aspirin is superior to warfarin alone for AF.

Many patients who are eligible for antithrombotic therapy remain unprotected, possibly because of prescriber concerns about the potential for hemorrhagic complications and the difficulty of managing oral anticoagulation. ASHP believes that the safe and effective use of warfarin is dependent on adequate patient education and monitoring—services that can be efficiently provided by pharmacists. ASHP encourages pharmacists to work actively with other health care providers to optimize anticoagulant therapy through the provision of these services.

Background

Atrial fibrillation is present in 2.3% of people over 40 years of age and in 5.9% of those over 65 years.[2] Most patients with AF are elderly (mean age, 75 years). Men are more likely to have AF than women during their lifetimes, but because more women than men live to age 75, equal numbers of men and women have AF.[2] The presence of valvular heart disease alone, especially rheumatic mitral valve disease, is associated with a significant increase in the risk of stroke and systemic embolism. Although never evaluated in a randomized trial, there is little doubt that long-term anticoagulant therapy is effective in reducing the frequency of systemic embolism in patients with rheumatic mitral valve disease and AF. It is strongly recommended, therefore, that warfarin therapy be used in patients with AF and rheumatic mitral valve disease.[3,4]

Table 1.
Recommendations on Antithrombotic Therapy in Chronic Atrial Fibrillation[a]

Age (yr)	Risk Factors[b]	Recommendation
<65	Yes	Warfarin to achieve INR[c] of 2–3
<65	No	Aspirin or nothing
65–75	Yes	Warfarin to achieve INR of 2–3
65–75	No	Warfarin to achieve INR of 2–3 or aspirin
>75	Yes or no	Warfarin to achieve INR of 2–3

[a]Adapted from reference 1, with permission.
[b]Risk factors for stroke include previous transient ischemic attack or stroke, hypertension, heart failure, diabetes, clinical coronary artery disease, mitral stenosis, prosthetic heart valves, and thyrotoxicosis.
[c]INR = International Normalized Ratio.

Nonrheumatic AF, usually defined as AF without evidence or a clinical history of mitral valve stenosis, afflicts about 2.2 million Americans, and the prevalence is higher in older age groups.[5–8] Nonrheumatic AF occurs most commonly in patients with hypertension or ischemic heart disease (coronary artery disease), hyperthyroidism, cardiomyopathy, and congestive heart failure. Consequently, this ASHP Therapeutic Position Statement focuses on nonrheumatic AF. Hereafter, the term "atrial fibrillation" ("AF") refers to nonrheumatic AF.

The risk of stroke in patients with AF is 5% per year, or five to six times higher than in an age-matched population without AF. Approximately 75,000 strokes occur each year in the United States in patients with AF.[1,9] The risk of stroke varies greatly depending on age and the presence of coexisting cardiovascular disease (appendix). In patients with AF, the major clinical risk factors for stroke are a history of hypertension, prior stroke or transient ischemic attack, recent heart failure, and thyrotoxicosis. Age and diabetes have also been identified in some studies as major risk factors. The annual event rate varies considerably depending on patient age and the presence of risk factors that were identified in an Atrial Fibrillation Investigators analysis.[11] Patients under the age of 65 years with no risk factors have an annual event rate of 0.3–3.1%. One or more risk factors increase the rate to 3.0–8.1% per year.[11] Among persons in the age range 65–75 years, the rates are 2.7–7.1% with no risk factors and 3.9–8.3% with one or more risk factors. Among persons older than 75 years, the annual risk ranges from 1.7% to 7.7% with no risk factors and from 4.7% to 13.9% with one or more risk factors. Analysis of placebo-treated patients in a large randomized clinical trial indicates that the annual rate of thromboembolism increases from 2.5% per year with no risk factors to 7.2% with one risk factor to 17.6% with two or more risk factors.[13] Therefore, stratification of patients on the basis of risk is useful for determining the best type of antithrombotic therapy.[13]

Thrombi that form in high-flow arteries are rich in platelets, and antiplatelet agents such as aspirin are thought to be optimal therapy. Because patients with AF frequently have vascular disease, thrombi may arise in high-flow areas such as the carotid circulation in addition to the cardiac chambers, and antiplatelet therapy may protect some patients in whom thrombi develop in this manner.[9,14] However, patients with AF may also develop thrombi in the atria, especially the atrial appendages, because of stasis or turbulent

blood flow. These cardiogenic emboli contain fewer platelets, are less responsive to antiplatelet therapy, and are best prevented by warfarin.

Patients with cardioembolic stroke typically have an abrupt onset of symptoms and die suddenly or are left with major neurologic sequelae. While the benefits of antithrombotic therapy in preventing stroke are well established, only about one quarter of patients with AF are receiving warfarin,[8] perhaps because of physician concerns about the small but important risk of serious hemorrhagic complications. It is therefore prudent that practitioners have a thorough understanding of the risks versus the benefits of this therapy.

The benefit of antithrombotic therapy can be expressed as the absolute risk reduction (difference in risk between the control group [x] and the treated group [y]; $x - y$) or the relative risk reduction (percent reduction in risk in the treated group [y] compared with the controls [x]; $[(x - y)/x] \times 100\%$). Comparing treatments by reporting only the relative risk ratio or the percent change in the event rate can be misleading. This is particularly true for antithrombotic therapy in AF, since the absolute risk of stroke varies widely, from about 1% with no risk factors to more than 15% with multiple risk factors (appendix).[13] A useful estimate of benefit can be calculated from the absolute risk reduction and expressed as the "number needed to treat" (NNT).[15] NNT is defined as the number of persons who need to be treated to prevent one event per year and is equal to 1/(treatment event rate–control event rate).

Evidence for Efficacy of Antithrombotic Therapy

Warfarin. There have been five randomized controlled trials of antithrombotic therapy for mostly primary prevention of stroke and systemic embolism in AF and one trial for secondary intervention (Table 2). Compared with placebo, warfarin reduces the relative risk of stroke by nearly 70% when the International Normalized Ratio (INR) target range is 1.5–4.5. If an on-therapy, or efficacy, analysis is used rather than an intention-to-treat analysis, the relative risk reduction is over 80%.[14] The absolute reduction in stroke risk by warfarin ranged from 2.5% per year to 4.7% per year in primary prevention studies and was 8.4% per year in the secondary intervention study (Table 2). This implies that 22–40 patients would need to be treated with warfarin to prevent one first-time stroke or systemic embolism per year. Prevention of one secondary event per year would require warfarin therapy in only 12 patients.

In a primary and secondary prevention trial, the efficacy of low-intensity, fixed-dose warfarin (INR, 1.2–1.5) plus aspirin (325 mg/day) was compared with that of conventional adjusted-dose warfarin therapy in high-risk AF patients.[22] Patients given adjusted-dose warfarin had a significantly lower rate of stroke and systemic embolism than patients given aspirin in combination with low-intensity warfarin therapy (1.9% per year versus 7.9% per year, or an absolute reduction in risk of 6.0% per year). Thus, 17 high-risk AF patients would need to be treated with adjusted-dose warfarin therapy to prevent one stroke not prevented by aspirin plus low-intensity warfarin therapy.[22] Reduction in disabling stroke by warfarin averaged only 1.5% per year in unselected AF patients.[11]

Intracranial hemorrhage during warfarin therapy in carefully monitored clinical trials occurs at a rate of 0.4–1.5% per year.[11,23] Thus, according to NNT analysis, one intracranial hemorrhage will occur per year for every 67–250 patients treated with warfarin. While the intracranial bleeding rate with warfarin is fairly low in low-risk patients, the absolute risk of intracranial hemorrhage may approach the absolute reduction in the risk of stroke. Knowledge of local trends in bleeding complications will help in balancing the risk with the benefit of anticoagulation. These principles should help clinicians more clearly discern the risk–benefit ratio of anticoagulants in a given patient and dispel their reluctance to prescribe this therapy in patients who would clearly benefit.

The risk–benefit ratios of warfarin treatment for chronic AF established in large clinical trials may not be generalizable to routine clinical practice because patients generally are more carefully selected and more intensively monitored in clinical trials.[11,24] Elderly persons over 75 years of age constitute the group of most concern. Several studies have shown that older patients may require smaller dosages of warfarin than younger patients to maintain a given level of anticoagulation and that they may be at greater risk for major hemorrhage.[25,27] Fihn, et al.[26] found that life-threatening and fatal complications were more common in patients 80 years of age or older (relative risk, 4.5; absolute event rate, 3.3% per year).

The optimal intensity of anticoagulation to adequately prevent stroke and minimize bleeding risk probably depends on the inherent stroke risk. In the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) and Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) primary prevention trials, low-intensity anticoagulation (estimated INR target range, 1.5–2.5) was highly effective for relatively low-risk patients.[17,19] In contrast, time-dependent analysis of warfarin efficacy in AF patients with prior stroke or transient ischemic attack suggested that more intensive anticoagulation (INR, 2.5–4.2) may be optimal.[22,28]

In a recent case–control study, Hylek, et al.[29] found that an INR of <2.0 was associated with an increased risk of ischemic stroke in patients with AF. This finding is useful for establishing the lower end of an INR range that should provide protection from stroke. The highest risk was for patients with an INR of <1.5. If patients are less than 75 years of age, an INR range of 2.0–3.0 is effective and safe; for some patients older than 75 years, the lower end of this range may be a reasonable target.

Recently, Palareti, et al.[27] found in a large cohort study that age was strongly correlated with the risk of major hemorrhage. The rate of major hemorrhage in patients over 70 years of age was four times that in patients ages 50–69 years. A higher target INR (2.5–4.0) may be considered for secondary intervention based largely on one large randomized trial.[28]

In summary, the current recommended range of intensity of anticoagulation in most patients with AF is an INR of 2.0–3.0.[1,11] Patients over the age of 75 who are at a higher risk of bleeding may require more intensive monitoring, and the need to lower the target INR to the lower half of the range of 2.0–3.0 should be considered in these patients.[22,26]

Aspirin. Aspirin is much less effective than warfarin in preventing stroke (primarily noncardioembolic stroke), and only the Stroke Prevention in Atrial Fibrillation (SPAF) study demonstrated a significant benefit from aspirin (Table 2).[10,30] However, in high-risk AF patients, the combination of aspirin and low-intensity fixed-dose warfarin (INR, 1.2–1.5)

Table 2.
Efficacy of Antithrombotic Therapy for Reducing Risk of Ischemic Stroke in Patients with Atrial Fibrillation[a]

Study	Type[b]	*n*	Target INR or Aspirin Dosage	Relative Risk Reduction, % (*p*)[c]	Absolute Risk Reduction (%/yr)	NNT
Warfarin versus Placebo						
AFASAK[16]	1°	671	2.8–4.2	58 (<0.05)	2.6	39
SPAF I[10]	1°	421	2.0–4.5[d]	65 (0.01)	4.7	22
BAATAF[17]	1°	420	1.5–3.0[d]	86 (0.002)	2.6	39
CAFA[18]	1°	378	2.0–3.0	33 (>0.05)	2.5	40
SPINAF[19]	1°	571	1.5–3.0[d]	79 (0.001)	3.4	30
EAFT[20]	2°	439	2.5–4.0	66 (0.001)	8.4	12
Aggregate[e]				68 (<0.001)		
Aspirin versus Placebo						
AFASAK[16]	1°	672	75 mg/day	18 (>0.05)	0.7	143
SPAF I[10]	1°	1120	325 mg/day	44 (0.01)	2.5	40
EAFT[20]	2°	782	300 mg/day	15 (>0.05)	1.3	77
Aggregate				21 (<0.05)		
Warfarin versus Aspirin						
SPAF II[21]	1°	1100	325 mg/day	31 (>0.05)	0.8	125
AFASAK[16]	1°	671	2.8–4.2, 75 mg/day	50 (0.05)	1.9	53
SPAF III[22]	1°	1044	2–3, 325 mg/day[f]	76 (0.001)	6.0	17
EAFT[20]	2°	455	2.5–4.0, 300 mg/day	62 (0.001)	6.4	16
Aggregate				55 (<0.01)		

[a]INR = International Normalized Ratio, NNT = number needed to treat to prevent one ischemic stroke per year, AFASAK = Atrial Fibrillation Aspirin Study of Anticoagulation from Kopenhaven, SPAF = Stroke Prevention in Atrial Fibrillation, BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation, CAFA = Canadian Atrial Fibrillation Anticoagulation, SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation, EAFT = European Atrial Fibrillation Trial.
[b]1° = primary prevention (in several studies, 5–10% of patients had remote thromboembolism), 2° = secondary intervention (previous transient ischemic attack or stroke).
[c]Reduction compared with control (active treatment or placebo) by intention-to-treat analysis.
[d]INR estimated for BAATAF, SPAF I, and SPINAF, which used prothrombin time ratios.
[e]Average of all studies cited.
[f]Aspirin 325 mg/day plus warfarin given to achieve an INR in the range of 1.2–1.5.

did not confer sufficient efficacy in stroke prevention, while conventional adjusted-dose warfarin therapy (INR, 2.0–3.0) demonstrated a significant reduction (absolute risk reduction of 6.0% per year) compared with low-intensity warfarin plus aspirin.[22]

The key in selecting antithrombotic prophylaxis is stroke risk stratification. While there is consensus in identifying high-risk patients,[11,22] risk stratification for low-risk patients remains controversial. Subgroups of low-risk AF patients have been proposed whose inherent stroke rate would be low (<2% per year) (appendix), but none of the stratification schemes has been satisfactorily validated in a randomized clinical trial. Patients with AF who are younger than 65 years and have no identifiable risk factors receive little benefit from warfarin (appendix), and if any therapy is provided, aspirin at a dosage of 325 mg/day is considered adequate (Table 1).[11] While aspirin has not been proved to be of value, specifically for other low-risk AF patients, it is reasonable because of its low toxicity and its potential benefit for associated, sometimes occult, coronary artery disease.

Cost-Effectiveness of Therapy

Antithrombotic prophylaxis for AF is considered to be cost-effective if the rate of thromboembolism is high relative to the rate of major bleeding events.[31] Using direct costs, Gage, et al.[32] found that for patients with AF and one additional risk factor, warfarin therapy cost $8000 per quality-adjusted life-year (QALY) saved. Patients with low risk of stroke (appendix) or lone AF were more costly to treat; the estimated cost of warfarin therapy was about $370,000 per QALY saved. For patients who were not prescribed warfarin, aspirin was preferred to no therapy on the basis of both quality-adjusted survival and cost in all cases, regardless of the number of risk factors present. Other investigators have also concluded that warfarin is cost-effective in high-risk patients with AF.[33,34] The Agency for Health Care Policy and Research has estimated that appropriate anticoagulant therapy in AF would save approximately $600 million annually in the prevention and treatment of stroke.[a]

Role of the Pharmacist

To optimize the safety and effectiveness of long-term oral anticoagulant therapy, the pharmacist should take an active role in educating and monitoring the patient. Patients should be adequately counseled on the full range of issues pertaining to anticoagulation, such as the indication for therapy, the laboratory test used to monitor anticoagulation, the need for close medical supervision, signs and symptoms of bleeding or thromboembolic complications, dietary interactions, drug interactions, alcohol consumption, and possible alterations in the response to warfarin in the presence of various underlying medical conditions. The pharmacist should also take an active role in closely monitoring and reporting newly observed adverse drug reactions and interactions. Long-term oral anticoagulant therapy should be regularly monitored by prothrombin time (PT) test, with conversion of the PT into the INR.[35,36] ASHP has previously endorsed the routine use of the INR for monitoring warfarin therapy.[36]

Safe and effective monitoring has been achieved through the establishment of specialty practice anticoagulation clinics, and there are numerous reports and trials that document the role of pharmacists in these clinics.[37–41] Clinics with personnel focused on anticoagulation therapy are capable of reducing hemorrhagic complication rates and thromboembolism rates compared with routine medical care (RMC).

Ansell and Hughes[38] recently summarized the literature relating to the outcome in patients undergoing anticoagulation therapy who were seen during RMC and in anticoagulation clinics (ACC) staffed by pharmacists and other health professionals. Their review showed that the rate of thromboembolism is reduced from 16.2% per patient-year in RMC to 2.4% per patient-year in ACC and that major hemorrhage is reduced from 10.9% to 2.8% per patient-year. Cost savings of $800 to $1600 per patient-year were also noted with ACC. Other studies conducted in pharmacist-run clinics support these findings.[39–41]

Pharmacists may also contribute to positive patient outcomes by helping to identify candidates for antithrombotic prophylaxis who are not receiving any form of therapy. Inpatients can be identified case by case or through screening of electrocardiograms. Inpatients and outpatients could be identified through diagnosis-related-group or International Classification of Diseases codes. Once patients are identified, pharmacists should encourage the appropriate use of warfarin and aspirin through one-on-one interactions and educational programs based on guidelines of the American College of Chest Physicians[1] and this ASHP Therapeutic Position Statement.

Summary

Stroke is a catastrophic, but largely preventable, consequence of AF. ASHP supports recommendations established by the American College of Chest Physicians (Table 1) for the use of antithrombotic therapy in appropriate patients to reduce the morbidity and mortality associated with stroke. The selection of warfarin versus aspirin should be based on the presence of clinical risk factors for stroke and the patient's ability to safely undergo anticoagulation therapy. Adequate patient education and monitoring are keys to the successful use of antithrombotic therapy, and ASHP believes that pharmacists can play an important role in providing these services.

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Appendix—Risk of Stroke in Atrial Fibrillation

Stroke Prevention in Atrial Fibrillation Study,[10] Placebo Group. High-risk variables were history of hypertension, prior stroke or transient ischemic attack (TIA), diabetes, and recent heart failure. With high-risk variables absent, the thromboembolic risk rate was 1.4% per year (95% confidence interval [CI], 0.05–3.7% per year). With high-risk variables present, the rate was >7% per year. The fraction of AF patients at low risk was 38%.

Pooled Data from Atrial Fibrillation Investigators.[11] High-risk variables were history of hypertension, prior stroke or TIA, diabetes, and age >65 years. With high-risk variables absent, the thromboembolic risk rate was 1.0% per year (95% CI, 0.3–3.1%). With high-risk variables present, the rate was >5% per year. The fraction of AF patients at low risk was 15%.

Stroke Prevention in Atrial Fibrillation Study, Aspirin Group.[12] High-risk variables were history of hypertension, prior stroke or TIA, women older than 75 years, and impaired left ventricular function (including recent congestive heart failure or fractional shortening of ≤25% on M-mode echocardiography). With high-risk variables absent, the thromboembolic risk rate was 1% per year (95% CI, 0.5–2.3%). With high-risk variables present, the rate was >6% per year. The fraction of AF patients at low risk was 30%.

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[a]Life-saving treatments to prevent stroke underused. Agency for Health Care Policy and Research news release. Washington, DC; 1995 Sep 7.

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