

# ASHP Therapeutic Position Statement on Antithrombotic Therapy in Chronic Atrial Fibrillation

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## Position

The American Society of Health-System Pharmacists (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.<sup>1</sup> Warfarin is more effective than aspirin but carries a higher risk of bleeding and requires regular medical and therapeutic monitoring.

ASHP supports recommendations established by the American College of Chest Physicians (ACCP) (Table 1) for the use of antithrombotic therapy in patients with AF to reduce the morbidity and mortality associated with stroke.<sup>1</sup> ASHP encourages the use of warfarin, if it can be ad-

ministered safely, in all patients with chronic AF who are younger than 75 years and have one or more clinical risk factors for stroke or who are older than 75 years. However, ASHP recognizes that for patients age 65–75 years 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 stroke prevention in AF.<sup>1</sup>

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.<sup>1</sup> ASHP believes that the safe and effective use of warfarin

is dependent on adequate patient education and monitoring, which are 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

AF is the most commonly encountered cardiac arrhythmia in clinical practice. It has been estimated that close to 2.5 million people in the United States currently have AF. By 2050, this number is expected to increase to more than 5.6 million.<sup>2,3</sup> The presence of AF is strongly related to age, occurring in 2.3% of people over age 40 years, 5% of people older than 65 years, and nearly 10% of individuals older than 80 years.<sup>2-4</sup> Given the predominance of AF among older patients and the aging of the U.S. population, the health care burden caused by AF is estimated to increase

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Table 1.  
**Recommendations for the Use of Antithrombotic Therapy in Chronic Atrial Fibrillation<sup>1</sup>**

Age (yr)	Risk Factors <sup>a</sup>	Recommendation <sup>b</sup>
>75	No	Warfarin
>75	Yes	Warfarin
65–75	No	Warfarin or aspirin 325 mg/day
65–75	Yes	Warfarin
<65	No	Aspirin 325 mg/day
<65	Yes	Warfarin

<sup>a</sup>The presence of one or more of the following risk factors is an indication for warfarin therapy: age > 75 years; prior ischemic stroke, transient ischemic attack, or systemic embolism; moderately or severely impaired left ventricular systolic function; congestive heart failure; hypertension; and diabetes mellitus.

<sup>b</sup>Target International Normalized Ratio for warfarin therapy is 2.5 (range, 2.0–3.0).

dramatically.<sup>5</sup> In fact, hospitalization rates attributable to AF have doubled to tripled in recent years.

AF is a strong independent risk factor for ischemic stroke.<sup>6</sup> Approximately 15% of all ischemic strokes in the United States can be attributed to AF.<sup>1</sup> The risk of stroke in patients with AF is four to five times higher than in an age-matched population without AF. This corresponds to an increased incidence of stroke of approximately 5% per year for primary events and 12% per year for secondary events.<sup>1,7</sup> As the risk of AF increases with advanced age, so does the risk of stroke attributable to AF. The frequency of stroke attributable to AF is 1.5% in patients age 50–59 years and 23.5% in patients 80–89 years.<sup>6</sup> Stroke caused by AF results in significant morbidity and mortality and poor quality of life in stroke survivors.<sup>2,8</sup> Worse outcomes with higher mortality and disability have been reported in patients with AF who have a stroke versus patients who have a stroke but do not have AF.<sup>9,10</sup>

For platelet-rich thrombi that form in high-flow arteries, antiplatelet agents such as aspirin are considered to be optimal therapy. Because patients with AF frequently have vascular disease, thrombi may arise in high-flow areas such as the carotid circulation and cardiac chambers, and antiplatelet therapy may protect some patients in whom thrombi

develop in this manner.<sup>7,11</sup> 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 anticoagulant therapy.<sup>1,7,11</sup>

Most strokes in patients with AF appear to be the result of cardiogenic embolism.<sup>1</sup> 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 25–50% of patients with AF are receiving warfarin,<sup>4,11–14</sup> perhaps because of physician concerns about the small (1–3%) but important risk of serious hemorrhagic complications. It is therefore prudent that practitioners have a thorough understanding of the risks and benefits of this therapy.

### Definitions

This therapeutic position statement is an update of the 1998 ASHP Therapeutic Position Statement on Antithrombotic Therapy in Chronic Atrial Fibrillation.<sup>15</sup> AF can be categorized as initial or acute (onset detected within 48 hours), paroxysmal (intermittent or terminated spontaneously on at least one occasion),

persistent (duration of >seven days and not terminated spontaneously), or permanent (resistant to pharmacologic or electrical cardioversion).<sup>16</sup> The chronic cardiac conditions most commonly associated with the development of AF are rheumatic mitral valve disease, coronary artery disease, congestive heart failure, and hypertension. Noncardiac etiologies, often reversible, include hyperthyroidism, hypoxic pulmonary conditions, surgery, and alcohol withdrawal. In up to a third of cases, no predisposing condition exists; this type of AF is called “lone AF.” The most predominant form of AF is nonvalvular AF.<sup>16</sup> This document focuses on nonvalvular AF, or AF not associated with rheumatic mitral valve disease or prosthetic heart valves. Hereafter, AF refers to nonvalvular AF.

The benefit of antithrombotic therapy for the prevention of stroke in patients with AF has been well established. This benefit can be expressed as the absolute risk reduction  $x-y$ , where  $x$  is the risk in the control group and  $y$  is the risk in the treated group, or as the relative risk reduction  $([x-y]/x) \times 100\%$ , where  $y$  and  $x$  are the percent reductions in risk in the treated and control groups, respectively. When comparing treatments, 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.<sup>17</sup> A useful estimate of benefit can be calculated from the absolute risk reduction and expressed as the number needed to treat (NNT).<sup>18</sup> The NNT is defined as the number of persons who must be treated to prevent one event per year and is equal to  $1/(\text{treatment event rate} - \text{control event rate})$ .

### Risk stratification

The risk of stroke varies greatly

depending on age, the presence of coexisting cardiovascular disease, and the presence of additional risk factors. Therefore, antithrombotic therapy must be tailored based on each patient's age, comorbidities, contraindications, and stroke risk. Several risk-stratification models have been developed using data from pooled analyses of the original antithrombotic treatment trials and expert consensus (Table 2). The most commonly cited risk-stratification schemes have been derived from the Atrial Fibrillation Investigators (AFI),<sup>19</sup> two analyses from the Stroke Prevention in Atrial Fibrillation (SPAF) investigators,<sup>20,21</sup> the Framingham score,<sup>22</sup> the CHADS<sub>2</sub> (Congestive Heart Failure, Hypertension, Age, Diabetes, and Stroke-doubled) score,<sup>23</sup> and the ACCP Consensus Guidelines on Antithrombotic and Thrombolytic Therapy.<sup>1</sup> Although there is some variation among the various risk-stratification models, the major risk factors tend to

overlap. The most commonly identified risk factors for stroke include older age, history of previous systemic thromboembolism, hypertension, female sex, congestive heart failure or left ventricular systolic dysfunction, elevated systolic blood pressure, and diabetes (Table 3).<sup>24</sup>

When determining a patient's composite stroke risk, it is important to note that the presence of various risk factors is additive and not mutually exclusive.<sup>21</sup> Patients with one or more risk factors in the AFI and SPAF trials had higher annual stroke rates (4.3–8.1% and 2.6–7.1%, respectively), depending on the number and type of risk factors.<sup>19,21</sup> The CHADS<sub>2</sub> risk-scoring system integrates factors from the AFI and the SPAF I–II schemes. The risk of stroke is increased with higher CHADS<sub>2</sub> scores (Table 4).<sup>23</sup> In a recent study, the CHADS<sub>2</sub> risk-scoring system demonstrated greater predictive value for stroke than the AFI, SPAF, Framingham, or ACCP criteria.<sup>25</sup>

Other recent efforts to compare the various risk-stratification schemes found that stroke rates varied among the schemes, with significant variation noted in the moderate-to-high-risk categories but more consistent rates in the low-risk categories.<sup>26</sup>

**Evidence for efficacy of antithrombotic therapy**

**Oral anticoagulation—warfarin.** Five randomized controlled trials of oral vitamin K antagonist therapy for primary prevention of stroke and systemic embolism in AF<sup>27-31</sup> and one trial for secondary intervention<sup>32,33</sup> have been published (Table 5). Patients with chronic persistent AF and patients with paroxysmal AF were included in these trials. Warfarin was the oral anticoagulant used in the primary prevention trials and phenprocoumon or acenocoumarol was used in the secondary prevention trial. There was variation between the target intensity of anticoagulation in the six trials. Although the definition

Table 2. Summary of the Main Stroke Risk-Stratification Schemes for Patients with Atrial Fibrillation<sup>a</sup>

Risk-Stratification Scheme	Risk Group <sup>b</sup>		
	High	Moderate	Low
ACCP <sup>1</sup>	Prior stroke, TIA, or systemic thromboembolism; age > 75 yr; hypertension; DM; moderate or severe LVSD and/or CHF	Age 65–75 yr with no other risk factors	Age < 65 yr with no other risk factors
ACC/AHA/ESC guidelines <sup>16</sup>	Prior stroke, TIA, embolism, mitral stenosis, prosthetic heart valve	Age ≥ 75 yr, hypertension, DM; CHF, LVSD (EF < 35%)	Age 65–74 yr, women, CAD, thyrotoxicosis
AFI <sup>19</sup>	Age ≥ 65 yr, history of hypertension, CAD, or DM	Age ≥ 65 yr, history of hypertension, CAD, or DM	Age < 65 yr, no high-risk features
SPAF <sup>20,21</sup>	Women age > 75 yr, SBP > 160 mm Hg, LVD	History of hypertension, no high-risk features	No history of hypertension, no high-risk features
Framingham <sup>22</sup>	...	...	...
CHADS <sub>2</sub> <sup>23,d</sup>	3–6	1–2	0

<sup>a</sup>Adapted from references 1, 7, and 16. ACCP = American College of Chest Physicians, TIA = transient ischemic attack, DM = diabetes mellitus, LVSD = left ventricular systolic dysfunction, CHF = coronary heart failure, ACC = American College of Cardiology, AHA = American Heart Association, ESC = European Society of Cardiology, EF = ejection fraction, CAD = coronary artery disease, AFI = Atrial Fibrillation Investigators, SPAF = Stroke Prevention in Atrial Fibrillation, SBP = systolic blood pressure, LVD = left ventricular dysfunction, CHADS<sub>2</sub> = Congestive Heart Failure, Hypertension, Age, Diabetes, and Stroke-doubled.

<sup>b</sup>The annual risk of stroke for the high-, moderate-, and low-risk groups is 8–12%, 4%, and 1%, respectively.

<sup>c</sup>Uses a weighted point scoring system, where the total score (maximum 31 points) corresponds to a predicted five-year stroke risk. Risk factors included older age, female sex, elevated blood pressure, and DM.

<sup>d</sup>Scheme assigns one point each for recent congestive heart failure, hypertension, age ≥ 75 years, and DM and two points for history of stroke or TIA.

Table 3. Independent Predictors of Stroke for Patients with Atrial Fibrillation<sup>a</sup>

Risk Factor	AFI <sup>19</sup>	SPAF <sup>20,21</sup>	Framingham Study <sup>22</sup>
Older age	+	+	+
Female		+	+
Prior ischemic stroke or TIA	+	+	+
Prior CHF or LVSD		+	
Hypertension	+	+	
Elevated systolic blood pressure			+
Diabetes mellitus	+		+

<sup>a</sup>Adapted from reference 24, with permission. AFI = Atrial Fibrillation Investigators, SPAF = Stroke Prevention in Atrial Fibrillation, TIA = transient ischemic attack, CHF = congestive heart failure, LVSD = left ventricular systolic dysfunction.

Table 4. Association between CHADS<sub>2</sub> Scores and Risk of Future Stroke<sup>a</sup>

CHADS <sub>2</sub> Score <sup>b</sup>	Adjusted Stroke Rate, % <sup>c</sup> (95% CI)
0	1.9 (1.2–3.0)
1	2.8 (2.0–3.8)
2	4.0 (3.1–5.1)
3	5.9 (4.6–7.3)
4	8.5 (6.3–11.1)
5	12.5 (8.2–17.5)
6	18.2 (10.5–27.4)

<sup>a</sup>Adapted from reference 23, with permission. CHADS<sub>2</sub> = Congestive Heart Failure, Hypertension, Age, Diabetes, and Stroke-doubled, CI = confidence interval.

<sup>b</sup>Scheme assigns one point each for recent congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus and two points for history of stroke or transient ischemic attack.

<sup>c</sup>Per 100 patient-years.

of primary outcome varied among the trials, all studies considered stroke a primary event. Due to the great benefit observed with oral anticoagulation, most of these trials were terminated early, and the numbers of events reported were fairly small. Compared with placebo, oral anticoagulation reduces the relative risk of stroke by nearly 70% when the International Normalized Ratio (INR) target range is 1.5–4.5 (Table 6).<sup>19</sup> If an efficacy analysis is used rather than an intent-to-treat analysis, the relative risk reduction is over 80%.<sup>41</sup>

The annual absolute reduction in stroke risk with warfarin was 2.5–4.7% in the primary prevention studies and 8.4% in the secondary intervention study (Table 5). 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. Anticoagulation was found to be effective in preventing strokes of all severities. Reduction in disabling stroke by warfarin averaged 1.5% per year in unselected AF patients.<sup>19</sup> The beneficial effect of warfarin on outcomes was maintained across all patient subgroups, and most of the strokes in the warfarin group occurred in patients who had an INR below the target range or who had stopped therapy. In the five primary prevention studies, the all-cause mortality rate was lowered by 33% in the anticoagulation-treated patients.<sup>19</sup> Taken together, this evidence supports the efficacy of oral anticoagulation therapy with war-

farin for stroke prevention in patients with AF.

**Aspirin.** Aspirin is much less effective than warfarin in preventing stroke (primarily cardioembolic stroke) (Tables 5 and 6).<sup>1</sup> Five studies have compared the efficacy of aspirin with placebo,<sup>27,29,32,34–36</sup> with the aspirin dosage ranging from 50 mg/day<sup>34</sup> to 325 mg/day<sup>29</sup> (Table 5). The only study that demonstrated a significant benefit from aspirin was the SPAF trial, in which a 42% relative risk reduction was reported.<sup>29</sup> Three trials found no significant benefit with aspirin versus placebo.<sup>27,32,34,35</sup> Another trial, Low-Dose Aspirin, Stroke, and Atrial Fibrillation (LASAF), found inconsistent effects of aspirin versus placebo, with significant benefit reported in patients receiving aspirin 125 mg every other day but no significant benefit in patients receiving aspirin 125 mg every day.<sup>36</sup> Pooled data from the three largest studies<sup>27,29,32</sup> resulted in a 21% relative risk reduction (95% confidence interval [CI], 0–38%) in favor of aspirin versus placebo<sup>42</sup> (Table 6). Another meta-analysis of aspirin versus placebo found similar results (22% risk reduction [95% CI, 2–38%]).<sup>43</sup>

**Oral anticoagulation versus aspirin.** The effect of vitamin K antagonists was compared with that of aspirin in six studies (Table 5).<sup>27,32,37–40</sup> Three of the trials<sup>27,32,38</sup> found significant benefit in favor of adjusted-dose warfarin (INR, 2.0–3.0), with relative risk reductions in primary events of 48%,<sup>27</sup> 40%,<sup>32</sup> and 74%.<sup>38</sup> The remaining three studies<sup>37,39,40</sup> found no significant difference between adjusted-dose oral anticoagulation and aspirin; however, one study<sup>39</sup> was stopped early in light of the results of SPAF III,<sup>38</sup> and another study<sup>40</sup> was limited by low event rates, which decreased the power of the analysis.

A meta-analysis found a benefit in favor of the vitamin K antagonists versus aspirin, with a relative risk reduction of 46% (95% CI, 29–57%)

**Table 5. Efficacy of Antithrombotic Therapy for Reducing Risk of Ischemic Stroke in Patients with Atrial Fibrillation: Summary of the Major Randomized Trials<sup>a</sup>**

Study	n	INR Range	Daily Aspirin Dose (mg)	No. Events/yr/100 pts		RRR <sup>b</sup> (%)	ARR (%) / yr	P
				Group 1	Group 2			
<b>OAC (group 1) vs. control (group 2)</b>								
AFASAK <sup>127</sup>	671	2.8–4.2	... <sup>c</sup>	2.7	6.2	56	3.5	<0.05
BAATAF <sup>28</sup>	420	1.5–2.7 <sup>d</sup>	...	0.4	3.0	86	2.6	0.002
SPAF <sup>129</sup>	421	2.0–4.5 <sup>d</sup>	...	2.3	7.4	67	5.1	0.01
SPINAF <sup>30</sup>	571	1.4–2.8 <sup>d</sup>	...	0.9	4.3	79	3.4	0.001
CAFA <sup>31</sup>	378	2.0–3.0	...	3.4	4.6	26	1.2	NS
EAFI <sup>32</sup>	439	2.5–4.0	...	8.5	16.5	47	8.0	0.001
<b>Aspirin (group 1) vs. control (group 2)</b>								
AFASAK <sup>127</sup>	672	...	75	5.2	6.2	16	1.0	NS
SPAF <sup>129</sup>	1120	...	325	3.6	6.3	42	2.7	0.02
EAFI <sup>32</sup>	782	...	300	15.5	19.0	17	3.5	0.12
ESPS II <sup>34,35</sup>	211	...	50	13.8	20.7	33	6.9	0.16
LASAF <sup>36</sup>	195	...	125	2.6	2.2	15	0.4	NS
	181	...	125 q.o.d.	0.7	2.2	68	1.5	0.05
<b>OAC (group 1) vs. aspirin (group 2)</b>								
AFASAK <sup>127</sup>	671	2.8–4.2	75	2.7	5.2	48	2.5	<0.05
EAFI <sup>32</sup>	455	2.5–4.0	300	NA	NA	40	NA	0.008
SPAF II <sup>37</sup>								
Age ≤ 75 yr	715	2.0–4.5	325	1.3	1.9	33	0.6	0.24
Age > 75 yr	385	2.0–4.5	325	3.6	4.8	27	1.2	0.39
SPAF III <sup>38</sup>	1044	2.0–3.0	325 <sup>e</sup>	1.9	7.9	74	6.0	<0.001
AFASAK II <sup>39</sup>	339	2.0–3.0	300	3.4	2.7	21	0.7	NS
PATAF <sup>40</sup>	272	2.5–3.5	150	2.5	3.1	19	0.6	NS

<sup>a</sup>INR = International Normalized Ratio, RRR = relative risk reduction, ARR = absolute risk reduction, OAC = oral anticoagulation, AFASAK = Atrial Fibrillation Aspirin Study of Anticoagulation from Copenhagen, BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation, SPAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation, SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation, CAFA = Canadian Atrial Fibrillation Anticoagulation, NS = not significant, EAFI = European Atrial Fibrillation Trial, ESFS = European Stroke Prevention Study, LASAF = Low-Dose Aspirin, Stroke and Atrial Fibrillation, PATAF = Primary Prevention of Arterial Thromboembolism in Nonrheumatic AF in Primary Care Trial.  
<sup>b</sup>Reduction compared with control (active treatment or placebo) using intent-to-treat analysis.  
<sup>c</sup>Not applicable.  
<sup>d</sup>INR estimated for BAATAF, SPAF I, and SPINAF, which used prothrombin time ratios.  
<sup>e</sup>Aspirin 325 mg/day plus warfarin given to achieve an INR of 1.2–1.5.

Table 6.  
**Efficacy of Antithrombotic Therapy in Atrial Fibrillation from Pooled Data of Randomized Trials<sup>a</sup>**

Treatment Comparison	RRR, % <sup>b</sup> (95% Confidence Interval)
Adjusted-dose oral anticoagulation vs. no antithrombotic therapy	68 (50–79)
Aspirin vs. no antithrombotic therapy	21 (0–38)
Adjusted-dose oral anticoagulation vs. aspirin	52 (37–63)

<sup>a</sup>Adapted from reference 1, with permission. RRR = relative risk reduction.

<sup>b</sup>Reduction in risk of ischemic stroke demonstrated by the first treatment mentioned.

for all strokes and 52% (95% CI, 37–63%) for ischemic stroke (Table 6).<sup>44</sup> However, there was a 1.7-fold increase in major bleeding reported (95% CI for hazard ratio, 1.21–2.41). In balancing the efficacy and safety of oral anticoagulation, treating 1000 AF patients for one year with adjusted-dose warfarin, compared with aspirin, would prevent 23 ischemic strokes and cause 9 additional major bleeding events.<sup>1</sup> Another meta-analysis showed similar results, with a 36% relative risk reduction in all strokes (95% CI, 14–52%) and a 46% reduction in ischemic stroke (95% CI, 27–60%) in favor of adjusted-dose warfarin versus aspirin.<sup>42</sup>

Overall, these data suggest that the benefit in stroke reduction in patients with AF is greater with warfarin than with aspirin (Table 6). While the benefit of aspirin diminishes as the stroke risk increases,<sup>42</sup> adjusted-dose warfarin is effective in preventing severe strokes and strokes of lesser severity.<sup>44,45</sup> It has been reported that strokes in patients with AF are more severe than strokes in non-AF patients.<sup>46</sup> However, warfarin therapy to achieve an INR of  $\geq 2.0$  is associated with better short-term survival if stroke occurs.<sup>47</sup>

**Combined therapy with oral anticoagulation and an antiplatelet agent.** In a primary and secondary prevention trial, the efficacy of low-intensity, fixed-dose warfarin (INR target of 1.2–1.5) plus aspirin (325

mg/day) was compared with that of conventional adjusted-dose warfarin therapy (INR target of 2.0–3.0) in high-risk AF patients.<sup>38</sup> 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, respectively)—an absolute reduction in risk of 6.0% per year. Thus, 17 high-risk AF patients must be treated with adjusted-dose warfarin therapy to prevent one stroke not prevented by aspirin plus low-intensity warfarin therapy.<sup>38</sup> No positive synergistic effect of the combination aspirin and low-intensity warfarin was observed in this study.<sup>38</sup> In another trial that combined low-intensity anticoagulation with aspirin, the combination regimen was also found ineffective in preventing strokes.<sup>39</sup> One additional study compared the combination of aspirin 100 mg/day and the anticoagulant fluindione (target INR of 2.0–2.6) with fluindione monotherapy (target INR of 2.0–2.6).<sup>48</sup> This study was stopped early due to increased bleeding complications in the group receiving combination therapy.

**Optimal intensity of anticoagulation therapy**

The optimal intensity of anticoagulation to adequately prevent stroke and minimize bleeding risk may depend on the inherent stroke

risk and bleeding risk. In two of the early primary prevention trials, the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)<sup>28</sup> and Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF),<sup>30</sup> low-intensity anticoagulation (estimated INR target range of 1.5–2.8) was found effective for relatively low-risk AF patients. However, low-intensity anticoagulation (target INR of 1.2–1.5), even when given in combination with aspirin (325 mg/day), was ineffective in high-risk AF patients in the SPAF III study.<sup>38</sup> Another trial found a higher INR intensity (INR goal 2.5–4.0) effective for secondary prevention in patients with a previous event, but a reduction in efficacy at INRs of  $< 2.0$  was also observed.<sup>33</sup>

In a meta-analysis of three AF stroke-prevention trials, adjusted-dose anticoagulation (INR goal of 2.0–3.0) was found to be more effective than fixed low-dose warfarin, with a relative risk reduction of 38% (95% CI, –20% to 68%).<sup>42</sup> In a case-control study, Hylek et al.<sup>49</sup> found that an INR of  $< 2.0$  was associated with an increased risk of ischemic stroke in patients with AF. The risk of stroke was two times higher at an INR of 1.7 and three times higher at an INR of 1.5 compared with the risk of stroke at an INR of 2.0. Event rates were even higher in patients with an INR of  $< 1.5$ . These findings were confirmed in another case-control study in which AF patients with an INR of  $< 2.0$  had an increased risk of stroke.<sup>50</sup> In addition, INRs of  $< 2.0$  have been linked to an increased risk of severe or fatal stroke.<sup>47</sup> These findings are useful for establishing the lower end of an INR range that should provide appropriate protection against stroke and severe stroke.

Although data from randomized trials comparing an INR of 1.5–2.0 with an INR of 2.0–3.0 and without the addition of aspirin are lacking, using an INR target of 2.0–3.0 would seem a reasonable standard as large randomized trials have used this

range successfully. Current evidence does not support lower INR targets in patients over age 75 years. As these patients have a higher risk of bleeding and stroke, careful monitoring and warfarin dosing to aim for strict INR control (goal of 2.5) are preferred. In patients deemed to have a higher risk of bleeding, aiming for the lower half of the target INR range of 2.0–3.0 may be a reasonable approach. The current ACCP recommended range of intensity of anticoagulation in patients with AF is an INR of 2.0–3.0.<sup>1</sup>

### Safety of antithrombotic therapy

Bleeding is the major complication associated with oral anticoagulation therapy. Although the definition of major bleeding varied slightly among the studies, generally an event was classified as such if it resulted in transfusion or hospitalization, caused death or permanent disability, or occurred in a critical anatomical location. In the pooled analysis<sup>19</sup> of five primary prevention trials,<sup>27–31</sup> there was no significant difference in the annual rate of major bleeding complications in patients treated with adjusted-dose anticoagulation versus patients who received placebo (1.3% versus 1.0%, respectively). The annual rate of intracranial hemorrhage (ICH) was 0.3% in the group receiving an oral anticoagulant and 0.1% in the control group.<sup>19</sup> ICH is of major concern, as it can cause complications that are considered greater than the ischemic strokes that the antithrombotic therapy is intended to prevent.

ICH during warfarin therapy in carefully monitored clinical trials occurs at a rate of 0.3–1.5% per year.<sup>19,51</sup> 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 ICH may approach the absolute reduction in the risk of stroke in warfarin-treated patients

at high risk for bleeding. Knowledge of patient-specific risk factors for bleeding complications will help in balancing the risks and benefits of anticoagulation. These principles should help clinicians more clearly discern the risk:benefit ratio of anticoagulants in a given patient and dispel the reluctance to prescribe this therapy in patients who would clearly benefit.

The risk:benefit ratio of warfarin treatment for chronic AF established in large clinical trials may not always be generalizable to routine clinical practice because patients generally are more carefully selected and more intensively monitored in clinical trials.<sup>19,52</sup> Persons over age 75 years constitute the group of most concern.<sup>53</sup> 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.<sup>52,54–56</sup> Fihn et al.<sup>54</sup> 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). Palareti et al.<sup>55</sup> also found 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 age 50–69 years. High INR values are also linked to increased rates of ICH at any age. An annual rate of ICH of >3% was reported in patients treated with anticoagulants, and this was strongly related to INRs of >4.0.<sup>57</sup> In addition, two large observational studies confirmed a drastic increase in ICH rates at INRs of >4.0.<sup>56,58</sup> In contrast, other reports have not found an association between advanced age and increased bleeding complications.<sup>59</sup> These controversial findings may be explained by the wide range in the mean age of patients enrolled in the various studies. One study reported that insufficient education about

oral anticoagulant therapy was a significant predictive factor for bleeding complications in older patients.<sup>60</sup> The safety of anticoagulants in clinical practice can be improved by the implementation of systematic monitoring and education programs, such as anticoagulation clinics and patient self-testing and management.<sup>59</sup> Recent data suggest that low rates of hemorrhage can be attained in clinical practice, even in elderly patients, if well-organized anticoagulation clinics are involved in the process of care for patients on warfarin.<sup>61,62</sup>

### Recommendations for the use of antithrombotic therapy in patients with chronic AF

Adjusted-dose oral anticoagulation therapy is an effective measure in decreasing the risk of ischemic stroke in patients with AF, and it is considerably more effective than aspirin. The risk of bleeding, including ICH, associated with oral anticoagulation is also higher than in patients treated with aspirin, and the management of patients taking warfarin therapy is more complex than it is for patients treated with aspirin. Patients at high risk of stroke gain a greater absolute benefit from warfarin therapy than patients with a lower risk. To this end, warfarin use has been recommended mainly for patients who have a moderate-to-high risk of stroke, where the benefits of therapy clearly outweigh the risk of bleeding and the burden of monitoring. Therefore, when selecting the optimal antithrombotic agent, the risk of stroke and hemorrhage and the ability to comply with therapy need to be considered and balanced in each patient's case.

Guidelines issued by ACCP<sup>1</sup>; the American College of Cardiology, the American Heart Association, and the European Society of Cardiology (ACC/AHA/ESC)<sup>16</sup>; and the American Academy of Family Physicians and the American College of Physicians (AAFP/ACP)<sup>63</sup> recommend

antithrombotic therapy based on various risk-stratification algorithms. Both the ACCP and ACC/AHA/ESC guidelines use an age-based, risk-stratification scheme and recommend either aspirin (81–325 mg) or warfarin, depending on the presence of additional risk factors (Tables 1 and 7). Although similar in some respects, the guidelines differ regarding (1) risk stratification and recommendations for moderate- and high-risk patients, (2) the INR target ranges for elderly patients (INR target of 2.0 [range, 1.6–2.5] recommended by the AHA guidelines in patients 75 years or older who have an increased risk of bleeding versus an INR target of 2.5 [range, 2.0–3.0]) recommended by ACCP for all patients who are candidates for warfarin therapy), and (3) the age threshold for patients at high risk of stroke (Tables 1, 2, and 7).<sup>1,16</sup> The AAFP/ACP guidelines recommend the use of adjusted-dose warfarin in all patients with AF unless they are at low risk of stroke or have a contraindication to therapy.<sup>63</sup> The differences in recommendations for antithrombotic therapy among these guidelines are mainly based on the variation in the available risk-stratification schemes. Opinion is especially divided on the use of oral anticoagulation for patients at moderate risk (3–5% per year) of stroke.

**Emerging treatment options**

There is a need for novel antithrombotic therapies that are effective

and safe in preventing strokes in patients with AF and that are more convenient to use in the clinical setting (no need for dosage adjustment or monitoring, lack of drug or food interactions) compared with warfarin. One class of drugs in development that appears to have some of these beneficial features are the oral direct thrombin inhibitors.<sup>64</sup> The first agent of this class, ximelagatran, did not gain approved labeling by the Food and Drug Administration in the United States and was withdrawn from the markets in several European countries due to concerns of hepatotoxicity with the drug. However, other agents of this class, such as dabigatran, are in Phase III development and may prove to be potential alternatives to warfarin.

Other agents that may prove beneficial for stroke prevention in patients with AF are the factor Xa inhibitors. Idraparinux, an extended-release derivative of fondaparinux, is a long-acting indirect inhibitor of factor Xa. AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients with Atrial Fibrillation), compared a weekly subcutaneous dose of idraparinux with adjusted-dose warfarin.<sup>65</sup> The trial was stopped early because of major and clinically relevant bleeding in the group receiving idraparinux ( $p < 0.0001$ ). Bleeding was more pronounced in the elderly and in patients with renal impairment. The primary efficacy end-

point (cumulative incidence of symptomatic thromboembolism) met the criteria for noninferiority (0.9% per patient-year with idraparinux and 1.3% per patient-year with warfarin,  $p = 0.007$ ).<sup>66</sup> The BOREALIS-AF study is now underway and will compare the neutralizable form of idraparinux (biotinylated idraparinux) to warfarin, with considerations for doing adjustments based on age and renal function. Various oral factor Xa inhibitors are also in development.

The combination of clopidogrel and aspirin has also been proposed as a potential treatment option, as this combination may allow for fixed-dose therapy without the need for therapeutic monitoring. This combination is currently being tested in ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events).<sup>67</sup> This trial is designed to assess the efficacy of combined aspirin plus clopidogrel versus either warfarin (ACTIVE W) or aspirin (ACTIVE A). However, the ACTIVE W part of this trial was stopped early because oral anticoagulation was found superior to the combination antiplatelet therapy in preventing vascular events (3.93% versus 5.6% annual risk, respectively) ( $p = 0.0003$ ).<sup>68</sup> The ACTIVE A part of the study is still in progress.

**Cost-effectiveness of therapy**

The economic burden associated with stroke in the United States is extraordinarily high, and, with the increasing number of elderly patients with AF, this burden is expected to grow in coming years. In the United States, the overall cost associated with strokes for 2006 was estimated by the AHA to be \$57.9 billion.<sup>69</sup> The total direct cost of AF-related strokes has been reported to be around \$8 billion.<sup>70</sup> The average cost of caring for a stroke patient in the first 12 weeks after an ischemic stroke is about \$14,000.<sup>71</sup> A large percentage of hospitalized patients with AF do

Table 7.  
**ACC/AHA/ESC Recommendations for the Use of Antithrombotic Therapy in Chronic Atrial Fibrillation<sup>16,a</sup>**

No. and Level of Risk Factors <sup>b</sup>	Recommended Therapy	Target INR (Range)
0	Aspirin 81–325 mg daily	
1 Moderate	Aspirin 81–325 mg daily or warfarin	2.5 (2.0–3.0)
>1 Moderate or ≥1 high	Warfarin	2.5 (2.0–3.0) <sup>c</sup>

<sup>a</sup>ACC = American College of Cardiology, AHA = American Heart Association, ESC = European Society of Cardiology, INR = International Normalized Ratio.

<sup>b</sup>See Table 2 for risk factors and risk-scoring criteria.

<sup>c</sup>If patient has mechanical valve, target INR should be >2.5.

not receive warfarin, and only about one third of those who receive warfarin have an INR in target range.<sup>72</sup> In AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management), 72% of patients who had an ischemic stroke had either discontinued anticoagulation or had an INR of <2.0.<sup>73</sup> A recently published economic model suggests a potential saving of \$2.5 billion in the United States if half of all patients with AF receiving inappropriate or no anticoagulation were appropriately managed.<sup>70</sup>

The benefits, risks, and costs associated with antithrombotic therapy need to be carefully considered and balanced when selecting the most appropriate treatment option for patients with AF. Cost-effectiveness modeling can serve as a useful guide in such situations. 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.<sup>74</sup> Using direct costs, Gage et al.<sup>75</sup> found that for patients with AF and one additional risk factor, the cost of warfarin therapy was \$8,000 per quality-adjusted life-year (QALY) saved. Patients with a low risk of stroke or with 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 patients with a moderate-to-high risk of AF.<sup>76-78</sup>

### Managing anticoagulant therapy

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.<sup>79</sup> 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.<sup>59</sup> ASHP has previously endorsed the routine use of the INR for monitoring warfarin therapy.<sup>80</sup>

Safe and effective therapy 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 and the value of these clinics.<sup>81-83</sup> Clinics with personnel focused on anticoagulation therapy management are capable of reducing hemorrhagic complication rates and thromboembolism rates compared with routine medical care (RMC). Ansell and Hughes<sup>84</sup> summarized the literature relating to the outcomes in patients undergoing anticoagulation therapy who were seen during RMC and in anticoagulation clinics staffed by pharmacists and other health professionals. Their review found that the rate of thromboembolism was reduced from 16.2% per patient-year in RMC to 2.4% per patient-year in anticoagulation clinics and that major hemorrhage was reduced from 10.9% per patient-year with RMC to 2.8% per patient-year with anticoagulation clinics. Cost savings of \$800–\$1600 per patient-year were also noted with anticoagulation clinics. Other studies conducted in pharmacist-run clinics support these findings.<sup>85,86</sup>

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 ACCP<sup>1</sup> and this ASHP therapeutic position statement.

### Summary

Stroke is a potentially catastrophic, but largely preventable, consequence of AF. ASHP supports recommendations established by ACCP (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 play an important role in providing these services.

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