

## Antithrombotic Therapy in Atrial Fibrillation\*

### American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This chapter about antithrombotic therapy in atrial fibrillation (AF) is part of the American College of Chest Physicians Evidence-Based Guidelines Clinical Practice Guidelines (8th Edition). Grade 1 recommendations indicate that most patients would make the same choice and Grade 2 suggests that individual patient's values may lead to different choices (for a full understanding of the grading see Guyatt et al, *CHEST* 2008; 133[suppl]:123S–131S). Among the key recommendations in this chapter are the following (all vitamin K antagonist [VKA] recommendations have a target international normalized ratio [INR] of 2.5; range 2.0–3.0, unless otherwise noted). In patients with AF, including those with paroxysmal AF, who have had a prior ischemic stroke, transient ischemic attack (TIA), or systemic embolism, we recommend long-term anticoagulation with an oral VKA, such as warfarin, because of the high risk of future ischemic stroke faced by this set of patients (Grade 1A). In patients with AF, including those with paroxysmal AF, who have two or more of the risk factors for future ischemic stroke listed immediately below, we recommend long-term anticoagulation with an oral VKA (Grade 1A). Two or more of the following risk factors apply: age > 75 years, history of hypertension, diabetes mellitus, moderately or severely impaired left ventricular systolic function and/or heart failure. In patients with AF, including those with paroxysmal AF, with only one of the risk factors listed immediately above, we recommend long-term antithrombotic therapy (Grade 1A), either as anticoagulation with an oral VKA, such as warfarin (Grade 1A), or as aspirin, at a dose of 75–325 mg/d (Grade 1B). In these patients at intermediate risk of ischemic stroke we suggest a VKA rather than aspirin (Grade 2A). In patients with AF, including those with paroxysmal AF, age ≤ 75 years and with none of the other risk factors listed above, we recommend long-term aspirin therapy at a dose of 75–325 mg/d (Grade 1B), because of their low risk of ischemic stroke. For patients with atrial flutter, we recommend that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (Grade 1C). For patients with AF and mitral stenosis, we recommend long-term anticoagulation with an oral VKA (Grade 1B). For patients with AF and prosthetic heart valves we recommend long-term anticoagulation with an oral VKA at an intensity appropriate for the specific type of prosthesis (Grade 1B). See *CHEST* 2008; 133(suppl):593S–629S. For patients with AF of ≥ 48 h or of unknown duration for whom pharmacologic or electrical cardioversion is planned, we recommend anticoagulation with an oral VKA, such as warfarin, for 3 weeks before elective cardioversion and for at least 4 weeks after sinus rhythm has been maintained (Grade 1C). For patients with AF of ≥ 48 h or of unknown duration undergoing pharmacological or electrical cardioversion, we also recommend either immediate anticoagulation with unfractionated IV heparin, or low-molecular-weight heparin (LMWH), or at least 5 days of warfarin by the time of cardioversion (achieving an INR of 2.0–3.0) as well as a screening multiplane transesophageal echocardiography (TEE). If no thrombus is seen, cardioversion is successful, and sinus rhythm is maintained, we recommend anticoagulation for at least 4 weeks. If a thrombus is seen on TEE, then cardioversion should be postponed and anticoagulation should be continued indefinitely. We recommend obtaining a repeat TEE before attempting later cardioversion (Grade 1B addressing the equivalence of TEE-guided vs non-TEE-guided cardioversion). For patients with AF of known duration < 48 h, we suggest cardioversion without prolonged anticoagulation (Grade 2C). However, in patients without contraindications to anticoagulation, we suggest beginning IV heparin or LMWH at presentation (Grade 2C). (*CHEST* 2008; 133:546S–592S)

**Key words:** antithrombotic; atrial fibrillation; mitral stenosis; prophylaxis; stroke

**Abbreviations:** ACTIVE-W = Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events–Warfarin; ACUTE = Assessment of Cardioversion Using Transesophageal Echocardiography; AF = atrial fibrillation; AFASAK = Atrial Fibrillation Aspirin and Anticoagulation; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; AFI = Atrial Fibrillation Investigators; AMADEUS = Atrial Fibrillation Trial of Monitored Adjusted Dose Vitamin-K Antagonist, Comparing Efficacy and Safety With Unadjusted SanOrg34006/idaraparinux; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged; CABG = coronary artery bypass grafting surgery; CAD = coronary artery disease; CAFA = Canadian Atrial Fibrillation Anticoagulation; CHADS<sub>2</sub> = Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke (doubled) risk scoring system; CI = confidence interval; DC = direct current; DVT = deep venous thrombosis; EAFT = European Atrial Fibrillation Trial; ESPS = European Stroke Prevention Study; FFAACS = Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontane trial; ICD-9 = International Statistical Classification of Diseases and Related Health Problems; ICH = intracranial hemorrhage; INR = international normalized ratio; ISCOAT = Italian Study on Complications of Oral Anticoagulant Therapy; ITT = intention-to-treat; JAST = Japan Atrial Fibrillation Stroke Trial; LAA = left atrial appendage; LMWH = low-molecular-weight heparin; LV = left ventricular; NASPEAF = National Study for Prevention of Embolism in Atrial Fibrillation; NICE = National Institute for Health and Clinical Excellence; NNT = number needed to treat for 1 year; NSR = normal sinus rhythm; NVAF = nonvalvular atrial fibrillation; OAC = oral anticoagulation; OT = on-treatment; PAF = paroxysmal atrial fibrillation; PATAF = Primary Prevention of Arterial Thromboembolism in Nonrheumatic AF in Primary Care Trial; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PIAF = Pharmacologic Intervention in Atrial Fibrillation Trial; PTR = prothrombin time ratio; PTT = partial thromboplastin time; PY = person-years; RACE = Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study; RCT = randomized clinical trial; RR = risk reduction; RRR = relative risk reduction; SAFT = Swedish Atrial Fibrillation Trial; SIFA = Studio Italiano Fibrillazione Atriale; SPAF = Stroke Prevention in Atrial Fibrillation; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation; SPIRIT = Stroke Prevention In Reversible Ischemia Trial; SPORTIF = Stroke Prevention Using an Oral Thrombin Inhibitor in Patients With AF; TEE = transesophageal echocardiography; TIA = transient ischemic attack; VKA = vitamin K antagonist; WASPO = Warfarin vs Aspirin for Stroke Prevention in Octogenarians With AF

## SUMMARY OF RECOMMENDATIONS

### 1.1 AF

#### 1.1.1. In patients with AF, including those with paroxysmal AF, who have had a prior ischemic stroke, TIA, or systemic embolism, we recom-

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**mend long-term anticoagulation with an oral vitamin K antagonist, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) because of the high risk of future ischemic stroke faced by this set of patients (Grade 1A). Timing of the initiation of VKA therapy after an acute ischemic stroke involves balancing the risk of hemorrhagic conversion with short-term risk of recurrent ischemic stroke and is addressed in the chapter by Albers et al in this supplement.**

**1.1.2. In patients with AF, including those with paroxysmal AF, who have two or more of the following risk factors for future ischemic stroke, we recommend long-term anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) because of the increased risk of future ischemic stroke faced by this set of patients (Grade 1A). Two or more of the following risk factors apply: (1) age > 75 years; (2) history of hypertension; (3) diabetes mellitus; and (4) moderately or severely impaired left ventricular systolic function and/or heart failure.**

Remark: Recommendations 1.1.1 and 1.1.2 correspond to a recommendation of oral VKA therapy for individuals with a score  $\geq 2$  using the CHADS<sub>2</sub> classification. For these and all other recommendations of long-term therapy in this chapter, *long-term* means lifelong unless a contraindication emerges.

**1.1.3. In patients with AF, including those with paroxysmal AF, with only one of the risk factors**

listed below, we recommend long-term anti-thrombotic therapy (Grade 1A), either as anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) (Grade 1A), or as aspirin, at a dose of 75 to 325 mg/d (Grade 1B). For these patients at intermediate risk of ischemic stroke, we suggest a VKA rather than aspirin (Grade 2A). This set of patients with AF is defined by having one of the following risk factors: (1) age > 75 years; (2) history of hypertension; (3) diabetes mellitus; or (4) moderately or severely impaired left ventricular systolic function and/or heart failure.

**1.1.4. In patients with AF, including those with paroxysmal AF, aged  $\leq$  75 years and with none of the other risk factors listed above, we recommend long-term aspirin therapy at a dose of 75 to 325 mg/d (Grade 1B) because of their low risk of ischemic stroke.**

*Underlying values and preferences:* Anticoagulation with oral VKAs, such as warfarin, has far greater efficacy than aspirin in preventing stroke, and particularly in preventing severe ischemic stroke, in AF. We recommend the option of aspirin therapy for lower risk groups in 1.1.3 and 1.1.4, above, estimating the absolute expected benefit of anticoagulant therapy may not be worth the increased hemorrhagic risk and burden of anticoagulation. Individual lower-risk patients may rationally choose anticoagulation over aspirin therapy to gain greater protection against ischemic stroke if they value protection against stroke much more highly than reducing risk of hemorrhage and the burden of managing anticoagulation. Our recommendations assume that the patient is not at high risk for bleeding and that good control of anticoagulation will occur.

Remarks: These recommendations apply to patients with persistent or paroxysmal AF and not to patients with a single brief episode of AF due to a reversible cause, such as an acute pulmonary infection. The optimal dose of aspirin for patients with AF is unclear. The largest effect of aspirin was seen in the first Stroke Prevention in Atrial Fibrillation (SPAF I) trial, which used aspirin at 325 mg/d.<sup>1</sup> However, generalizing from trials of aspirin for all antithrombotic indications and from physiologic studies, we feel the best balance of efficacy and safety is achieved at low doses of aspirin, *ie*, 75 to 100 mg/d (see chapter on “Antiplatelet Drugs” in this supplement).<sup>2</sup>

## 1.2 Atrial Flutter

**1.2. For patients with atrial flutter, we recommend that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (Grade 1C).**

## 1.3 Valvular Heart Disease and AF

**1.3.1. For patients with AF and mitral stenosis, we recommend long-term anticoagulation with an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0) [Grade 1B].**

**1.3.2. For patients with AF and prosthetic heart valves we recommend long-term anticoagulation with an oral VKA, such as warfarin, at an intensity appropriate for the specific type of prosthesis (Grade 1B). See chapter on “Valvular and Structural Heart Disease” in this supplement.**

## 1.4 AF Following Cardiac Surgery

**1.4. For patients with AF occurring shortly after open-heart surgery and lasting  $\geq$  48 h, we suggest anticoagulation with an oral VKA, such as warfarin, if bleeding risks are acceptable (Grade 2C). The target INR is 2.5 (range, 2.0 to 3.0). We suggest continuing anticoagulation for 4 weeks following reversion to and maintenance of normal sinus rhythm (NSR), particularly if patients have risk factors for thromboembolism (Grade 2C).**

### 2.1 Anticoagulation for Elective Cardioversion of AF

**2.1.1. For patients with AF of  $\geq$  48 h or of unknown duration for whom pharmacologic or electrical cardioversion is planned, we recommend anticoagulation with an oral VKA, such as warfarin, at a target INR of 2.5 (range, 2.0 to 3.0) for 3 weeks before elective cardioversion and for at least 4 weeks after sinus rhythm has been maintained (Grade 1C).**

Remark: This recommendation applies to all patients with AF, including those whose risk factor status would otherwise indicate a low risk for stroke. Patients with risk factors for thromboembolism should continue anticoagulation beyond 4 weeks unless there is convincing evidence that sinus rhythm is maintained. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

**2.1.2. For patients with AF of  $\geq$  48 h or of unknown duration who are undergoing pharmacologic or electrical cardioversion, we recommend either immediate anticoagulation with IV unfractionated heparin (target partial thromboplastin time [PTT], 60 s; range, 50 to 70 s), or LMWH (at full deep venous thrombosis [DVT] treatment doses), or at least 5 days of warfarin (target INR of 2.5; range, 2.0 to 3.0) at the time of cardioversion and performance of a screening multiplane TEE. If no thrombus is seen, cardioversion is successful, and sinus rhythm is**

maintained, we recommend anticoagulation (target INR, 2.5; range, 2.0 to 3.0) for at least 4 weeks. If a thrombus is seen on TEE, then cardioversion should be postponed and anticoagulation should be continued indefinitely. We recommend obtaining a repeat TEE before attempting later cardioversion (all Grade 1B addressing the equivalence of TEE-guided vs non-TEE-guided cardioversion; see recommendation 2.1.1, above).

Remark: The utility of the conventional and TEE-guided approaches is likely comparable. This recommendation applies to all patients with AF, including those whose risk factor status would otherwise indicate a low risk for stroke. Patients with risk factors for thromboembolism should continue anticoagulation beyond 4 weeks unless there is convincing evidence that sinus rhythm is maintained. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

**2.1.3. For patients with AF of known duration < 48 h, we suggest that cardioversion be performed without prolonged anticoagulation (Grade 2C). However, in patients without contraindications to anticoagulation, we suggest beginning IV heparin (target PTT, 60 s; range, 50 to 70 s) or LMWH (at full DVT treatment doses) at presentation (Grade 2C).**

Remark: For patients with risk factors for stroke, it is particularly important to be confident that the duration of AF is < 48 h. In such patients with risk factors, a TEE-guided approach (see 2.12, above) is a reasonable alternative strategy. Postcardioversion anticoagulation is based on whether the patient has experienced more than one episode of AF and on his or her risk factor status. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

**2.1.4. For emergency cardioversion in the hemodynamically unstable patient, we suggest that IV unfractionated heparin (target PTT of 60 s with a target range of 50 to 70 s) or low-molecular-weight heparin (at full DVT treatment doses) be started as soon as possible, followed by at least 4 weeks of anticoagulation with an oral VKA, such as warfarin (target INR of 2.5; range, 2.0 to 3.0) if cardioversion is successful and sinus rhythm is maintained (Grade 2C).**

Remark: Long-term continuation of anticoagulation is based on whether the patient has experienced more than one episode of AF and on his or her risk factor status. For patients experiencing more than one episode of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

**2.1.5. For cardioversion of patients with atrial flutter, we suggest use of anticoagulants in the same way as for cardioversion of patients with AF (Grade 2C).**

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder and is an important independent risk factor for ischemic stroke. AF affects nearly two and a half million people in the United States.<sup>3,4</sup> Its prevalence is strongly dependent on age. AF is uncommon among individuals < 50 years old. Its frequency rises rapidly from the sixth decade onward, reaching a prevalence of nearly 10% in those > 80 years old.<sup>3-8</sup> Analyses from the Framingham Study indicate that the lifetime risk of AF for an individual age 40 years is about 25%.<sup>9</sup> The occurrence of AF may be even higher given the potential for AF to remain undiagnosed. The median age of patients with AF is approximately 72 years. AF is more prevalent in men than in women at all ages.<sup>3,5-7</sup> Because of the projected aging of the United States population, the number of individuals with AF is likely to increase substantially in coming decades.<sup>3,10</sup>

The rate of ischemic stroke among patients with AF included in primary prevention clinical trials and not treated with antithrombotic therapy averaged 4.5% per year, similar to estimates of stroke risk from the Framingham Heart Study.<sup>11,12</sup> AF increases the risk of stroke 4-5-fold, across all age groups.<sup>12</sup> As a consequence of its increasing prevalence, AF becomes an increasingly important cause of stroke with advancing age. In the Framingham Study, the percentage risk of stroke attributable to AF rose from 1.5% in the age group 50 to 59 years to 23.5% in the age group 80 to 89 years.<sup>13</sup> Overall, AF accounts for about 15% of all strokes in the United States.

Stroke in AF appears to be predominantly the result of cardiogenic embolism. This is based on clinical assessment, by extension of operative findings of intracardiac thrombus in patients with rheumatic mitral valve disease, and more recently, by transesophageal echocardiography (TEE) imaging of thrombus in the left atrium of patients with AF, mainly in the left atrial appendage.<sup>14-16</sup> Trials of anticoagulant and antiplatelet medications to prevent stroke in AF were conducted to interrupt the presumed cardioembolic mechanism of stroke in AF.

This chapter deals primarily with stroke prevention in nonvalvular AF when the dysrhythmia is not associated with rheumatic mitral valve disease or prosthetic heart valves. At least one recent trial studied patients with rheumatic mitral valve disease and its findings were quite similar to results in patients with nonrheumatic heart disease.<sup>17</sup> Further discussion of management of antithrombotic therapy in AF patients with valvular heart disease and prosthetic heart valves is provided in the chapter by

Salem et al in this supplement. Also excluded from the following recommendations are patients with transient, self-limited AF associated with acute illness. Table 1 describes the general structure of the studies considered in developing each of the recommendations that follow. Additional details on individual studies are provided in each section and in Tables 2–4.

## 1.0. ANTITHROMBOTIC THERAPY FOR AF OR ATRIAL FLUTTER: ANTICOAGULANTS AND ANTIPLATELET AGENTS

### 1.1 AF

#### 1.1.1. Efficacy of Oral Anticoagulant Therapy

*Results of a Systematic Review of Randomized Trials of Oral VKA Therapy vs No Antithrombotic Therapy:* Investigators from the five primary prevention trials pooled their data after standardizing clinical definitions. The individual studies and their results are summarized in Tables 2–4. Table 4, in particular, presents rates of standard relevant outcome events that may not have been the primary trial

outcome events chosen by study investigators. The results of individual-subject metaanalyses of these trials and later trials whose data were also pooled are provided in Table 5. The clinical trials included patients with chronic sustained (also categorized as “persistent” or “permanent” AF)<sup>18</sup> or, less commonly, paroxysmal (“intermittent”) AF. In most instances, AF had been present for many months to years. Each of these trials stopped early because of the large effect of oral anticoagulants in preventing ischemic stroke and systemic embolism (the CAFA trial stopped early because of the superiority of anticoagulation seen in other trials).<sup>19</sup> Because of this, the number of outcome events observed was relatively small, resulting in fairly wide confidence limits around estimates of efficacy. The intention-to-treat analysis of these pooled data revealed a reduction in annual stroke rate from 4.5% for the control patients and 1.4% for the patients assigned to adjusted-dose warfarin. The efficacy of warfarin was consistent across studies with an overall relative risk reduction of 68% (95% confidence interval [CI], 50 to 79%) analyzed by

**Table 1—Antithrombotic Therapy in AF: Core Elements of Design and Subject Eligibility (Section: Introduction)\***

Section	Population	Intervention or Exposure	Outcomes/Safety	Methodology	Exclusion Criteria†
1.1.	AF	Oral anticoagulation (fixed and adjusted dose), antiplatelet agents, and their combination	Stroke, other systemic embolism, major hemorrhage, and other fatal and nonfatal cardiovascular events	RCTs and observational studies	Patients with rheumatic heart disease or mechanical heart valves excluded in most studies; otherwise, over all studies nearly all categories of AF patient included, though individual studies vary
1.2.	Atrial flutter	Adjusted-dose anticoagulation	Stroke, other systemic embolism, major hemorrhage, and other fatal and nonfatal cardiovascular events	Observational studies	None
1.3.	AF and valvular disease	Adjusted-dose OAC	Stroke, other systemic embolism, major hemorrhage, and other fatal and nonfatal cardiovascular events	RCTs and observational studies	None
1.4.	AF	Alternative intensities of anticoagulant therapy	Stroke, other systemic embolism, major hemorrhage, and other fatal and nonfatal cardiovascular events	RCTs and observational studies	None
2.0.	Cardioversion of AF	Adjusted-dose anticoagulation; TEE guided vs conventional anticoagulation strategy	Stroke, other systemic embolism, major hemorrhage, and other fatal and nonfatal cardiovascular events; NSR	RCTs and observational studies	None
2.2.	AF	Anticoagulation in association with a rate control vs rhythm control strategy	All-cause death, stroke, other systemic embolism, major hemorrhage, and other fatal and nonfatal cardiovascular events	RCTs	None

\*See text and following tables for more detailed descriptions of individual studies.

†Major indication or contraindication to tested therapy is always an exclusion criterion.

**Table 2—AF Trials (Section: Introduction)\***

Study/yr	Total No. of Patients	Treatment Arms					Mean Follow-up, yr	Primary Outcome Measure
		Control	Full-Dose OAC, INR Range	Aspirin or Other Drug, mg/d	OAC Plus ASA	Low-Dose OAC		
AFASAK 1 <sup>22</sup> /1989	1,007	Yes	2.8–4.2	75			1.2	S, SE, TIA, ICH
BAATAF <sup>23</sup> /1990	420	Yes	1.5–2.7†				2.2	S
SPAF 1 <sup>1</sup> /1991	1,330	Yes	2.0–4.5†	325			1.3	S, SE
CAFA <sup>19</sup> /1991	383	Yes	2.0–3.0				1.3	S, SE, ICH, FH
SPINAF <sup>24</sup> /1992	525	Yes	1.4–2.8†				1.8	S
EAF <sup>20</sup> /1993	1,007	Yes	2.5–4.0	300			2.3	S, SE, MI, VD, ICH
SPAF II <sup>25</sup> /1994	1,100		2.0–4.5	325			2.7	S, SE
SPAF III <sup>26</sup> /1996	1,044		2.0–3.0		ASA 325 mg + warfarin (INR 1.2–1.5)		1.1	S, SE
SIFA <sup>60</sup> /1997	916		2.0–3.5	400‡			1.0	S, SE, MI, VD, PE, ICH
ESPS 2 <sup>46,47</sup> §/1997	429	Yes		50			1.1	S
AFASAK 2 <sup>54</sup> /1998	677		2.0–3.0	300	ASA 300 mg + warfarin 1.25 mg	Warfarin 1.25 mg	NA	S, SE, ICH
Pengo et al <sup>61</sup> /1998	303		2.0–3.0			Warfarin 1.25 mg	1.2	S, SE, ICH, FH, VD
LASAF <sup>45</sup> ¶/1999	285	Yes		125.62.5#			1.5	S, ICH
PATAF <sup>55</sup> /1999	729		2.5–3.5	150		Coumarin (INR 1.1–1.6)	2.7	S, SE, MH, VD
Japanese NVA <sup>250</sup> /2,000 (Secondary Prevention)	115		2.2–3.5			Warfarin (INR 1.5–2.1)	1.8	S, SE, TIA
FFAAC <sup>63</sup> /2001	157		2.0–2.6		ASA 100 mg + fluindione (INR 2.0–2.6)		0.8	S, SE, MI, ICH, VD
NASPEAF <sup>17</sup> /2004								
Higher risk	495		2.0–3.0		Triflusal 600 mg + acenocoumarol (INR 1.4–2.4)		2.9**	S, SE, TIA, ICH, VD
Lower risk	714		2.0–3.0	Triflusal 600 mg	Triflusal 600 mg + acenocoumarol (INR 1.25–2.0)		2.6**	S, SE, TIA, ICH, VD
Edvardsson et al <sup>50</sup> /2003	668	Yes			ASA 75 mg + warfarin 1.25 mg		2.8	S, ICH
SPORTIF III <sup>30</sup> /2003	3,410		2.0–3.0	Ximelagatran 36 mg bid			1.5	S, NSE, ICH
SPORTIF V <sup>31</sup> /2003	3,922		2.0–3.0	Ximelagatran 36 mg bid			1.7	S, NSE, ICH
ACTIVE W <sup>32</sup> /2006	6,706		2.0–3.0	ASA 75–100 mg + clopidogrel 75 mg			1.3**	S, NSE, MI, VD, ICH
JAST <sup>49</sup> /2006	871	Yes		150–200			2.1	S, TIA, VD
Hu et al <sup>53</sup> /2006	704		2.0–3.0	150–160			1.6	S, VD
BAFTA <sup>52</sup> /2007	973		2.0–3.0	75			2.7	S, NSE, ICH

\*ASA = aspirin; S = ischemic stroke; NSE = non-CNS systemic embolus; MH = major hemorrhage; FH = fatal hemorrhage; MI = myocardial infarction; VD = vascular death; NA = not available.

†Prothrombin time ratio-based target range: INR range is estimated.

‡Indobufen 200 mg bid (not aspirin).

§ESPS-2 also included two other treatment groups: (1) modified-release dipyridamole 200 mg bid; (2) aspirin, 25 mg bid plus modified-release dipyridamole 200 mg bid.

||This represents only the patients in ESPS-2 with AF.

¶Primary outcome not specified; however, sample size calculated using S + ICH.

#LASAF evaluated two doses of aspirin: 125 mg qd and 125 mg qod.

\*\*Median.

**Table 3—AF Trials: Primary Outcome Event Rates (Section: Introduction)**

Variables	Annual Rate per 100	RRR	Reported p Values
OAC vs control	OAC	Control	
AFASAK I <sup>*22</sup> /1989	2.7	6.2	56%
SPAF I <sup>1</sup> /1991	2.3	7.4	67%
BAATAF <sup>23</sup> /1990	0.4	3.0	86%
CAFA <sup>19</sup> /1991	3.4	4.6	26%
SPINAF <sup>24</sup> /1992	0.9	4.3	79%
EAFI <sup>20</sup> /1993	8.5	16.5	47%
ASA vs control	ASA	Control	
AFASAK I <sup>*22</sup> /1989	5.2	6.2	16%
SPAF I <sup>1</sup> /1991	3.6	6.3	42%
EAFI <sup>20</sup> /1993	15.5	19.0	17%
ESPS 2† <sup>46</sup> /1996 <sup>47</sup> /1997	13.8	20.7	33%
LASAF <sup>45</sup> /1999			
125 mg qd	2.6	2.2	(15%)
125 mg qod	0.7	2.2	68%
JAST <sup>49</sup> /2006	3.1	2.4	(50%)
OAC vs ASA	OAC	ASA	
AFASAK I <sup>*22</sup> /1989	2.7	5.2	48%
SPAF II <sup>25</sup> /1994:			
≤ 75	1.3	1.9	33%
> 75	3.6	4.8	27%
EAFI <sup>20</sup> /1993	NA	NA	40%
AFASAK 2 <sup>29</sup> /1999	3.4	2.7	(21%)
PATAF <sup>55</sup> /1999	2.5	3.1	19%
Hu et al <sup>53</sup> /2006	2.7	6.0	56%
BAFTA <sup>52</sup> /2007	1.8	3.8	52%
OAC vs low-dose OAC + ASA	OAC	OAC+ASA	
SPAF III <sup>28</sup> /1996	1.9	7.9	74%
AFASAK 2 <sup>29</sup> /1999	3.4	3.2	(6%)
NASPEAF <sup>17</sup> /2004 (triflusal, not ASA)‡			
Higher risk	4.6	2.3	(50%)
Lower risk	2.5	0.92	(63%)
OAC vs low-dose OAC	OAC	Low-dose OAC	
AFASAK 2 <sup>29</sup> /1999	3.4	3.9	13%
PATAF <sup>55</sup> /1999	2.5	2.2	(12%)
PENGO <sup>61</sup> /1998	3.6	6.2	42%
Japanese NVAF <sup>250</sup> /2000	1.1	1.7	35%
OAC vs indobufen	OAC	Indobufen	
SIFA <sup>60</sup> /1997	9.0	10.6	15%
OAC vs OAC+ASA	OAC	OAC+ASA	
FFAACs <sup>53</sup> /2001	2.9	7.9	63%
Low-dose OAC+ASA vs control	Low-dose OAC+ASA	Control	
Edvardsson et al <sup>50</sup> /2003	3.5	4.5	22%
OAC vs ximelagatran	OAC	Ximelagatran	
SPORTIF III <sup>30</sup> /2003	2.3	1.6	(30%)
SPORTIF V <sup>31</sup> /2005	1.2	1.6	25%
OAC vs ASA+clopidogrel	OAC	ASA+clopidogrel	
ACTIVE W (combined outcome) <sup>32</sup> /2006	3.9	5.6	31%
ACTIVE W (ischemic stroke) <sup>32</sup> /2006	1.0	2.2	54%

\*Based on intention-to-treat analysis.

†ESPS-2 had two additional treatment arms: dipyridamole 400 mg qd (annual stroke rate 15.1%); and dipyridamole 400 mg qd plus aspirin 50 mg qd (annual stroke rate 11.0%).

‡NASPEAF lower-risk group treated with triflusal 600 mg/d alone had an annual rate of primary outcome events of 3.8 per 100.

§Noninferiority criterion met; standard p values not applicable.<sup>59,281</sup>

||RRR is given in parentheses when the risk is reduced by the comparator.

intention-to-treat.<sup>11</sup> The absolute risk reduction implies that 31 ischemic strokes will be prevented each year for every 1,000 patients treated (or 32 patients needed to treat for 1 year to prevent one stroke, NNT = 32) [Table 5].

The percentage of strokes classified as moderate, severe, or fatal ranged between 43% and 64% across trials. Anticoagulation was effective for preventing strokes of all severities. The effect of warfarin was consistent across all patient subgroups. The majority

**Table 4—AF Trials: Rates of Standard Relevant Outcomes (Not Necessarily the Primary Outcomes of the Study, see Table 3)**  
 [Section: Introduction]\*

Study/yr	Interventions	Patients Analyzed/ Patients Randomized, No.	Person-Years of Follow up, No.†	Mortality Annual Rate/ 100 Rate Ratio (95% CI)	Stroke‡ Annual Rate/100 Rate Ratio (95% CI)	Systemic Emboli Annual Rate/100 Rate Ratio (95% CI)	Major Hemorrhage§ Annual Rate/100 (95% CI)	ICH   Annual Rate/100 Rate Ratio (95% CI)
<b>OAC vs control</b>								
AFASAK-1¶/ 1989 <sup>22</sup>	OAC: warfarin (INR 2.8–4.2) Control: placebo	OAC: 335/335 Control: 336/ 336	OAC: 413 Control: 398	NA	OAC: 11/413 = 2.7 Control: 19/398 = 4.8 RR: 0.56 (0.27–1.17)	OAC: 0/413 = 0 Control: 2/398 = 0.5 RR: 0	OAC: 2/413 = 0.5 Control: 0/398 = 0 RR: NA	OAC: 1/413 = 0.2 Control: 0/398 = 0 RR: NA
BAATAF <sup>23</sup> / 1990	OAC: warfarin (INR 1.5–2.7#) Control: no treatment	OAC: 212/215 Control: 208/213	OAC: 487 Control: 435	OAC: 11/487 = 2.3 Control: 26/435 = 6.0 RR: 0.38 (0.19–0.76)	OAC: 2/487 = 0.4 Control: 13/435 = 3.0 RR: 0.14 (0.03–0.61)	OAC: 0/487 = 0 Control: 0/435 = 0 RR: NA	OAC: 2/487 = 0.4 Control: 1/435 = 0.2 RR: 1.79 (0.16 – 19.70)	OAC: 1/487 = 0.2 Control: 0/435 = 0 RR: NA
SPAF 1 <sup>1</sup> /1991	OAC: warfarin (INR 2.0–4.5#) Control: placebo	OAC: 210/210 Control: 211/211	OAC: 260 Control: 244	OAC: 6/260 = 2.3 Control: 8/244 = 3.3 RR: 0.70 (0.24–2.03)	OAC: 6/260 = 2.3 Control: 17/244 = 7.0 RR: 0.33 (0.13–0.84)	OAC: 0/260 = 0 Control: 1/244 = 0.4 RR: 0	OAC: 4/260 = 1.5 Control: 4/244 = 1.6 RR: 0.94 (0.23–3.75)	OAC: 2/260 = 0.8 Control: 2/244 = 0.8 RR: 0.94 (0.13–6.66)
CAFA <sup>19</sup> /1991	OAC: warfarin (INR 2.0–3.0) Control: placebo	OAC: 187/189 Control: 191/194	OAC: 237 Control: 241	OAC: 12/237 = 5.1 Control: 8/241 = 3.3 RR: 1.53 (0.62–3.73)	OAC: 6/237 = 2.5 Control: 9/241 = 3.7 RR: 0.68 (0.24–1.90)	OAC: 1/237 = 0.4 Control: 2/241 = 0.8 RR: 0.51 (0.05–5.61)	OAC: 5/237 = 2.1 Control: 2/241 = 0.8 RR: 2.54 (0.49–13.10)	OAC: 1/237 = 0.4 Control: 0/241 = 0 RR: NA
SPINAF <sup>24</sup> / 1992	OAC: warfarin (INR 1.4–2.8#) Control: placebo	OAC: 260/269 Control: 265/269	OAC: 456 Control: 439.6	OAC: 16/456 = 3.5 Control: 23/439.6 = 5.2 RR: 0.67 (0.35–1.27)	OAC: 4/456 = 0.9 Control: 19/439.6 = 4.3 RR: 0.20 (0.07–0.60)	OAC: 2/456 = 0.4 Control: 1/439.6 = 0.2 RR: 1.93 (0.17–21.26)	OAC: 7/456 = 1.5 Control: 4/439.6 = 0.9 RR: 1.69 (0.49–5.76)	OAC: 1/456 = 0.2 Control: 0/439.6 = 0 RR: NA
EAFI <sup>20</sup> /1993	OAC: phenprocoumon or acenocoumarol (INR 2.5–4.0) Control: placebo	OAC: 225/225 Control: 214/214	OAC: 507 Control: 405	OAC: 41/507 = 8.1 Control: 44/405 = 10.9 RR: 0.74 (0.49–1.14)	OAC: 20/507 = 3.9 Control: 50/405 = 12.3 RR: 0.32 (0.19–0.54)	OAC: 1/507 = 0.2 Control: 4/405 = 1.0 RR: 0.20** (0.02–1.79)	OAC: 13/507 = 2.6 Control: 3/405 = 0.7 RR: 3.46 (0.99–12.15)	OAC: 0/507 = 0 Control: 1/405 = 0.2 RR: 0
<b>ASA vs control</b>								
AFASAK 1 <sup>22</sup> / 1989	ASA: 75 mg/d Control: placebo	ASA: 336/336 Control: 336/336	ASA: 409 Control: 398	NA	ASA: 16/409 = 3.9 Control: 19/398 = 4.8 RR: 0.82 (0.42–1.59)	ASA: 2/409 = 0.5 Control: 2/398 = 0.5 RR: 0.97 (0.14–6.91)	ASA: 1/409 = 0.2 Control: 0/398 = 0 RR: NA	ASA: 0/409 = 0 Control: 0/398 = 0 RR: NA
SPAF 1 <sup>1</sup> /1991	ASA: 325 mg/d Control: no treatment	ASA: 552/552 Control: 568/568	ASA: 720 Control: 731	ASA: 39/720 = 5.4 Control: 50/731 = 6.8 RR: 0.79 (0.52–1.20)	ASA: 42/731 = 5.7 Control: 42/731 = 5.7 RR: 0.56 (0.33–0.92)	ASA: 3/720 = 0.4 Control: 4/731 = 0.5 RR: 0.76 (0.17–3.40)	ASA: 10/720 = 1.4 Control: 14/731 = 1.9 RR: 0.73 (0.32–1.63)	ASA: 2/720 = 0.3 Control: 2/731 = 0.3 RR: 1.02 (0.14–7.21)
EAFI <sup>20</sup> /1993	ASA: 300 mg/d Control: placebo	ASA: 404/404 Control: 378/378	ASA: 838 Control: 715	ASA: 102/838 = 12.2 Control: 99/715 = 13.8 RR: 0.88 (0.67–1.16)	ASA: 88/838 = 10.5 Control: 90/715 = 12.6 RR: 0.83 (0.62–1.12)	ASA: 6/838 = 0.7 Control: 9/715 = 1.3 RR: 0.57** (0.20–1.60)	ASA: 6/838 = 0.7 Control: 4/715 = 0.6 RR: 1.28 (0.36–4.54)	ASA: 2/838 = 0.2 Control: 1/715 = 0.1 RR: 1.71 (0.15–18.82)
ESPS 2††/ 1996 <sup>47</sup> / 1997 <sup>46</sup>	ASA: 50 mg/d Control: placebo	ASA: 104/104 Control: 107/107	ASA: 123 Control: 111.4	NA	ASA: 17/123 = 13.8 Control: 23/111.4 = 20.7 RR: 0.67 (0.36–1.25)	NA NA	NA NA	NA NA

**Table 4—Continued**

Study/yr	Interventions	Patients Analyzed/ Randomized, No.	Person-Years of Follow up, No.†	Mortality Annual Rate/ 100 Rate Ratio (95% CI)	Stroke‡ Annual Rate/100 Rate Ratio (95% CI)	Systemic Emboli Annual Rate/100 Rate Ratio (95% CI)	Major Hemorrhage§ Annual Rate/100 (95% CI)	ICH   Annual Rate/100 Rate Ratio (95% CI)
LASAF (125 mg qd) <sup>45/</sup> 1999	ASA: 125 mg/d Control: placebo	ASA: 104/104 Control: 91/91	ASA: 145.3 Control: 134.6	ASA: 7/145.3 = 4.8 Control: 9/134.6 = 6.7 RR: 0.72 (0.27–1.93)	ASA: 4/145.3 = 2.8 Control: 3/134.6 = 2.2 RR: 1.24 (0.28–5.52)	NA	NA	NA
LASAF (125 mg qod) <sup>45/</sup> 1999	ASA: 125 mg qod Control: placebo	ASA: 90/90 Control: 91/91	ASA: 147.9 Control: 134.6	ASA: 3/147.9 = 2.0 Control: 9/134.6 = 6.7 RR: 0.30 (0.08–1.12)	ASA: 1/147.9 = 0.7 Control: 3/134.6 = 2.2 RR: 0.30 (0.03–2.92)	NA	NA	NA
JAST <sup>49/</sup> 2006	ASA: 150–200 mg/d Control: no treatment	ASA: 426/426 Control: 445/445	ASA: 896 Control: 936	ASA: 10/896 = 1.1 Control: 9/936 = 1.0 RR: 1.16 (0.47–2.86)	ASA: 17/896 = 1.9 Control: 18/936 = 1.9 RR: 0.99 (0.51–1.91)	ASA: 0/896 = 0 Control: 1/936 = 0.1 RR: 0	ASA: 7/896 = 0.8 Control: 2/936 = 0.2 RR: 3.66 (0.76–17.60)	ASA: 4/896 = 0.4 Control: 2/936 = 0.2 RR: 2.09 (0.38–11.41)
<b>OAC vs ASA</b>								
AFASAK 1 <sup>22/</sup> 1989	OAC: warfarin (INR 2.8–4.2) ASA: 75 mg/d	OAC: 335/335 ASA: 336/336	OAC: 413 ASA: 409	NA	OAC: 11/413 = 2.7 ASA: 16/409 = 3.9 RR: 0.68 (0.32–1.47)	OAC: 0/413 = 0 ASA: 2/409 = 0.5 RR: 0	OAC: 2/413 = 0.5 ASA: 1/409 = 0.2 RR: 1.98 (0.18–21.84)	OAC: 1/413 = 0.2 ASA: 0/409 = 0 RR: NA
SPAF II <sup>25</sup> (≤ 75 yr old)/1994	OAC: warfarin (INR 2.0–4.5) ASA: 325 mg/d	OAC: 358/358 ASA: 357/357	OAC: 1,099 ASA: 1,083	OAC: 36/1099 = 3.3 ASA: 41/1,083 = 3.8 RR: 0.87 (0.55–1.35)	OAC: 13/1099 = 1.2 ASA: 19/1,083 = 1.8 RR: 0.67 (0.33–1.37)	OAC: 1/1099 = 0.1 ASA: 2/1,083 = 0.2 RR 0.49 (0.04–5.43)	OAC: 1.7%/yr†† ASA: 0.9%/yr RR: 1.89	OAC: 6/1099 = .5 ASA: 2/1083 = .2 RR: 2.96 (0.60–14.65)
SPAF II (> 75 yr old) <sup>25/</sup> 1994	OAC: warfarin (INR 2.0–4.5) ASA: 325 mg/d	OAC: 197/197 ASA: 188/188	OAC: 394 ASA: 377	OAC: 26/394 = 6.6 ASA: 24/377 = 6.4 RR: 1.04 (0.60–1.81)	OAC: 13/394 = 3.3 ASA: 18/377 = 4.8 RR: 0.69 (0.34–1.41)	OAC: 1/394 = 0.3 ASA: 0/377 = 0 RR: NA	OAC: 4.2%/yr†† ASA: 1.6%/yr RR: 2.63	OAC: 7/394 = 1.8 ASA: 3/377 = 0.8 RR: 2.23 (0.58–8.63)
AFASAK 2 <sup>26/</sup> 1998	OAC: warfarin (INR 2.0–3.0) ASA: 325 mg/d	OAC: 170/170 ASA: 169/169	OAC: 355 ASA: 365	OAC: 17/355 = 4.8 ASA: 14/365 = 3.8 RR: 1.25 (0.62–2.53)	OAC: 10/355 = 2.8 ASA: 9/365 = 2.5 RR: 1.14 (0.46–2.81)	OAC: 2/355 = 0.6 ASA: 3/365 = 0.8 RR: 2.06 (0.19–22.68)	OAC: 2/355 = 0.6 ASA: 5/365 = 1.4 RR: 0.82 (0.22–3.06)	OAC: 2/355 = 0.6 ASA: 1/365 = 0.3 RR: 2.06 (0.19–22.68)
PATAF <sup>55/</sup> 1999	OAC: phenprocoumon or acenocoumarol (INR 2.5–3.5) ASA: 150 mg/d	OAC: 131/131 ASA: 141/141	OAC: 400.9 ASA: 392	OAC: 12/400.9 = 3.0 ASA: 17/392 = 4.3 RR: 0.69 (0.33–1.45)	OAC: 3/400.9 = 0.7 ASA: 4/392 = 1.0 RR: 0.73 (0.16–3.28)	OAC: 1/400.9 = 0.2 ASA: 1/392 = 0.3 RR: 0.98 (0.06–15.63)	OAC: 1/400.9 = 0.2 ASA: 1/392 = 0.3 RR: 0.98 (0.06–15.63)	OAC: 1/400.9 = 0.2 ASA: 1/392 = 0.3 RR: 0.98 (0.06–15.63)
Hu et al <sup>52/</sup> 2006	ASA: 150 mg/d OAC: warfarin (INR 2.0–3.0)	OAC: 369/369 ASA: 335/335	OAC: 584 ASA: 530	OAC: 4/584 = 0.7 ASA: 8/530 = 1.5 RR: 0.45 (0.14–1.51)	OAC: 6/584 = 1.0 ASA: 17/530 = 3.2 RR: 0.32 (0.13–0.81)	OAC: 13/584 = 2.2 ASA: 22/530 = 4.1 RR: 0.54 (0.27–1.06)	OAC: 5/584 = 0.9 ASA: 0/530 = 0 RR: NA	OAC: 3/584 = 0.5 ASA: 0/530 = 0 RR: NA
BAFTA <sup>62/</sup> 2007	ASA: 150–160 mg/d OAC: warfarin (INR 2.0–3.0) ASA: 75 mg/d	OAC: 488/488 ASA: 485/485	OAC: 1,318 ASA: 1,310	NA	OAC: 21/1318 = 1.6 ASA: 44/1,310 = 3.4 RR: 0.47 (0.28–0.80)	OAC: 1/1318 = 0.1 ASA: 3/1,310 = 0.2 RR: 0.33 (0.03–3.19)	OAC: 25/1,318 = 1.9 ASA: 25/1,310 = 1.9 RR: 0.99 (0.57–1.73)	OAC: 8/1318 = 0.6 ASA: 6/1310 = 0.5 RR: 1.33 (0.46–3.82)
<b>OAC vs low-dose OAC+ASA</b>								
SPAF III <sup>25/</sup> 1996	OAC: warfarin (INR 2.0–3.0) Low-dose OAC (warfarin INR 1.2–1.5) + 325 mg/d ASA	OAC: 523/523 OAC+ASA: 521/ 521	OAC: 581 OAC+ASA: 558	OAC: 35/581 = 6.0 OAC+ASA: 42/558 = 7.5 RR: 0.80 (0.51–1.25)	OAC: 11/581 = 1.9 OAC+ASA: 43/558 = 7.7 RR: 0.25 (0.13–0.48)	OAC: 0/581 = 0 OAC+ASA: 1/558 = 0.2 RR: 0	OAC: 12/581 = 2.1 OAC+ASA: 13/558 = 2.3 RR: 0.89 (0.40–1.94)	OAC: 3/581 = 0.5 OAC+ASA: 5/558 = 0.9 RR: 0.58 (0.14–2.41)

**Table 4—Continued**

Study/yr	Interventions	Patients Analyzed/ Patients Randomized, No.	Person-Years of Follow up, No.†	Mortality Annual Rate/100 Rate Ratio (95% CI)	Stroke‡ Annual Rate/100 Rate Ratio (95% CI)	Systemic Emboli Annual Rate/100 Rate Ratio (95% CI)	Major Hemorrhage§ Annual Rate/100 (95% CI)	ICH   Annual Rate/100 Rate Ratio (95% CI)
AFASAK II <sup>29</sup> / 1998	OAC: warfarin (INR 2.0–3.0) Low-dose OAC (warfarin 1.25 mg/d) + 300 mg/d ASA	OAC: 170/170 OAC+ASA: 171/ 171	OAC: 355 OAC+ ASA: 377	OAC: 17/355 = 4.8 OAC+ASA: 9/377 = 2.4 RR: 2.01 (0.89–4.50)	OAC: 10/355 = 2.8 OAC+ASA: 11/377 = 2.9 RR: 0.97 (0.41–2.27)	OAC: 2/355 = 0.6 OAC+ASA: 1/377 = 0.27 RR: 2.1 (0.19–23.42)	OAC: 4/355 = 1.1 OAC+ASA: 1/377 = 0.27 RR: 4.2 (0.47–38.01)	OAC: 2/355 = 0.6 OAC+ASA: 0/377 = 0 RR: NA
NASPEAF high-risk cohort <sup>17</sup> / 2004	OAC: Acenocumarol (INR 2.0–3.0) Low-dose OAC (acenocumarol INR 1.4–2.4) + 600 mg/d triflusal	OAC: 247/259 OAC+ASA: 223/ 236	OAC: 609.7 OAC+ ASA: 573.1	OAC: 23/609.7 = 3.8 OAC+ASA: 12/573.1 = 2.1 RR: 1.8 (0.90–3.62)	OAC: 12/609.7 = 2.0 OAC+ASA: 10/573.1 = 1.7 RR: 1.13 (0.49–2.61)	OAC: 2/609.7 = 0.33 OAC+ASA: 0/573.1 = 0 RR: NA	OAC: 13/609.7 = 2.1 OAC+ASA: 12/573.1 = 2.1 RR: 1.0 (0.46–2.23)	OAC: 5/609.7 = 0.8 OAC+ASA: 2/573.1 = 0.3 RR: 2.35 (0.46–12.11)
NASPEAF intermediate- risk cohort <sup>17</sup> / 2004	OAC: Acenocumarol (INR 2.0–3.0) Low-dose OAC (acenocumarol INR 1.4–2.4) + 600 mg/d Triflusal	OAC: 232/237 OAC+ASA: 222/ 235	OAC: 556.1 OAC+ ASA: 540.8	OAC: 20/556.1 = 3.6 OAC+ASA: 6/540.8 = 1.1 RR: 3.2 (1.30–8.07)	OAC: 6/556.1 = 1.1 OAC+ASA: 3/540.8 = 0.6 RR: 1.94 (0.49–7.78)	OAC: 0/556.1 = 0 OAC+ASA: 0/540.8 = 0 RR: NA	OAC: 10/556.1 = 1.8 OAC+ASA: 5/540.8 = 0.92 RR: 1.95 (0.66–5.69)	OAC: 4/556.1 = 0.7 OAC+ASA: 1/540.8 = 0.2 RR: 3.89 (0.43–34.80)
<b>OAC vs low-dose OAC</b>								
AFASAK II <sup>29</sup> / 1998	OAC: warfarin (INR 2.0–3.0) Low-dose OAC warfarin 1.25 mg/d	OAC: 170/170 Low-dose OAC: 167/167	OAC: 355 Low-dose OAC: 363	OAC: 17/355 = 4.8 Low-dose OAC: 6/363 = 1.7 RR: 2.90 (1.14–7.35)	OAC: 10/355 = 2.8 Low-dose OAC: 13/363 = 3.6 RR: 0.79 (0.34–1.79)	OAC: 2/355 = 0.6 Low-dose OAC: 1/363 = 0.28 RR: 2.0 (0.19–22.55)	OAC: 4/355 = 1.1 Low-dose OAC: 3/363 = 0.83 RR: 1.4 (0.31–6.09)	OAC: 2/355 = 0.6 Low-dose OAC: 1/363 = 0.3 RR: 2.17 (0.19–22.55)
PATAF <sup>55</sup> /1999	OAC warfarin (INR 2.5–3.5) Low-dose OAC: warfarin (INR 1.1–1.6)	OAC: 131/131 Low-dose OAC: 122/122	OAC: 400.9 Low-dose OAC: 361.1	OAC: 12/400.9 = 3.0 Low-dose OAC: 8/361.1 = 2.2 RR: 1.35 (0.55–3.31)	OAC: 3/400.9 = 0.7 Low-dose OAC: 4/361.1 = 1.1 RR: 0.68 (0.15–3.02)	OAC: 1/400.9 = 0.2 Low-dose OAC: 2/361.1 = 0.6 RR: 0.45 (0.04–4.97)	OAC: 1/400.9 = 0.2 Low-dose OAC: 1/361.1 = 0.3 RR: 0.90 (0.06–14.40)	OAC: 1/400.9 = 0.2 Low-dose OAC: 1/361.1 = 0.3 RR: 0.90 (0.06–14.40)
Pengo et al <sup>61</sup> / 1998	OAC: warfarin (INR 2.0–3.0) Low-dose OAC (warfarin 1.25 mg/d)	OAC: 152/153 Low-dose OAC: 147/150	OAC: 181.1 Low-dose OAC: 178.9	OAC: 6/181.1 = 3.3 Low-dose OAC: 7/178.9 = 3.9 RR: 0.85 (0.28–2.52)	OAC: 0/181.1 = 0 Low-dose OAC: 5/178.9 = 2.8 RR: 0	OAC: 2/181.1 = 1.1 Low-dose OAC: 0/178.9 = 0 RR: NA	OAC: 4/181.1 = 2.2 Low-dose OAC: 1/178.9 = .6 RR: 3.95 (0.44–35.34)	OAC: 1/181.1 = .6 Low-dose OAC: 0/178.9 = 0 RR: NA

**Table 4—Continued**

Study/yr	Interventions	Patients Analyzed/ Patients Randomized, No.	Person-Years of Follow up, No.†	Mortality Annual Rate/ 100 Rate Ratio (95% CI)	Stroke‡ Annual Rate/100 Rate Ratio (95% CI)	Systemic Emboli Annual Rate/100 Rate Ratio (95% CI)	Major Hemorrhage§ Annual Rate/100 (95% CI)	ICH   Annual Rate/100 Rate Ratio (95% CI)
Japanese NVAIF <sup>28/</sup> 2000	OAC: warfarin (INR 2.2–3.5) Low-dose OAC: warfarin (INR 1.5–2.1)	OAC: 55/55 Low-dose OAC: 60/60	OAC: 99.2 Low-dose OAC: 108.2	NA Low-dose OAC: 2/108.2 = 1.8 RR: 0.55 (0.05–6.01)	OAC: 1/99.2 = 1.0§ Low-dose OAC: 2/108.2 = 1.8 RR: 0.55 (0.05–6.01)	NA	OAC: 6/99.2 = 6.1 Low-dose OAC: 0/108.2 = 0 RR: NA	OAC: 2/99.2 = 2.0 Low-dose OAC: 0/108.2 = 0 RR: NA
<b>OAC vs indobufen</b>								
SIFA <sup>30/1997</sup>	OAC: (INR 2.0–3.5) Indobufen: 200 mg bid standard or 100 mg bid in patients with impaired renal function	OAC: 454/454 Indobufen: 462/ 462	OAC: 454 Indobufen: 462	OAC: 32/454 = 7.0 Indobufen: 35/462 = 7.6 RR: 0.93 (0.58–1.50)	OAC: 18/454 = 4.0 Indobufen: 23/462 = 5.0 RR: 0.80 (0.43 – 1.48)	OAC: 5/454 = 1.1    Indobufen: RR: 1.27 (0.34 – 4.74)	OAC: 8/454 = 1.8 Indobufen: 1/462 = 0.2 RR: 8.14 (1.02–65.09)	OAC: 4/454 = 0.9 Indobufen: 1/462 = 0.2 RR: 4.07 (0.46–36.42)
<b>OAC vs OAC + ASA</b>								
FFAAC <sup>63/</sup> 2001	OAC+placebo: fluidione (INR 2.0–2.6) OAC+ASA: fluidione (INR 2.0–2.6) ASA 100 mg/d	OAC+placebo: 81/81 OAC+ASA: 76/76	OAC+placebo: 69.66 OAC+ASA: 63.08	OAC+placebo: 3/69.66 = 4.3 OAC+ASA: 3/63.08 = 4.8 RR: 0.91 (0.18–4.49)	OAC+ Placebo: 0/69.66 = 0 OAC+ASA: 1/63.08 = 1.6 RR: 0	OAC+ Placebo: 1/69.66 = 1.4 OAC+ASA: 1/63.08 = 1.6 RR: 0.91 (0.06–14.48)	OAC+placebo: 1/69.66 = 1.4 OAC+ASA: 3/63.08 = 4.8 RR: 0.30 (0.03–2.90)	NA
<b>Low-dose OAC + ASA vs control</b>								
Edvardsson et al <sup>30/2003</sup>	Low-dose OAC+ ASA: warfarin 1.25 mg/d plus ASA 75 mg/d Control: no treatment	Low-dose OAC +ASA: 334/334 Control: 334/334	Low-dose OAC +ASA: 918.5 Control: 918.5	Low-dose OAC +ASA: 32/918.5 = 3.5 Control: 36/918.5 = 3.9 RR: 0.86 (0.53–1.39)	Low-dose OAC +ASA: 32/918.5 = 3.5 Control: 41/918.5 = 4.5 RR: 0.78 (0.49–1.24)	Low-dose OAC +ASA: 5/918.5 = 0.5 Control: 5/918.5 = 0.5 RR: 1.00 (0.29–3.45)	Low-dose OAC +ASA: 2/918.5 = 0.2 Control: 2/918.5 = 0.2 RR: 1.00 (0.14–7.10)	
<b>OAC vs ximelagatran</b>								
SPORTIF III <sup>30/2003</sup>	OAC: warfarin (INR 2.0–3.0); Ximelagatran: 36 mg bid	OAC: 1,703/1,703##; OAC: Ximelagatran: 1,704/1,704	OAC: 2,440; Ximelagatran: 2,446	OAC: 79/2,440 = 3.2; Ximelagatran: 78/2,446 = 3.2 RR: 1.02 (0.74–1.39)	OAC: 54/2,440 = 2.2; Ximelagatran: 36/2,446 = 1.5 RR: 1.50 (0.99–2.29)	OAC: 2/2,440 = 0.1; Ximelagatran: 4/2,446 = 0.2 RR: 0.50 (0.09–2.74)	OAC: 50/2,440 = 2.0***; Ximelagatran: 33/2,446 = 1.3 RR: 1.52 (0.98–2.36)	OAC: 9/2,440 = 0.4; Ximelagatran: 4/2,446 = 0.2 RR: 2.26 (0.69–7.32)

Table 4—Continued

Study/yr	Interventions	Patients Analyzed/ Patients Randomized, No.	Person-Years of Follow up, No.†	Mortality Annual Rate/100 Rate Ratio (95% CI)	Stroke‡ Annual Rate/100 Rate Ratio (95% CI)	Systemic Emboli Annual Rate/100 Rate Ratio (95% CI)	Major Hemorrhage§ Annual Rate/100 (95% CI)	ICH   Annual Rate/100 Rate Ratio (95% CI)
SPORTIF V <sup>31</sup> / 2005	OAC: warfarin (INR 2.0–3.0); Ximelagatran: 36 mg bid	OAC: 1,962/1,962; Ximelagatran: 1,960/1,960	OAC: 3,212; Ximelagatran: 3,193	OAC: 123/3,212 = 3.8; Ximelagatran: 116/3,193 = 3.6 RR: 1.05 (0.82–1.36)	OAC: 38/3,212 = 1.2; Ximelagatran: 47/3,193 = 1.5 RR: 0.80 (0.52–1.23)	OAC: 1/3,212 = 0.0; Ximelagatran: 6/3,193 = 0.2 RR: 0.17 (0.02–1.38)	OAC: 93/3,212 = 2.9††† Ximelagatran: 70/ 3,193 = 2.2 RR: 1.32 (0.97–1.80)	OAC: 9/3,212 = 0.3; Ximelagatran: 7/3,193 = 0.2 RR: 1.28 (0.48–3.43)
<b>OAC vs ASA + clopidogrel</b>								
ACTIVE W <sup>32</sup> / 2006	OAC: choice of OAC (INR 2.0–3.0) ASA + clopidogrel: ASA 75–100 mg/ d clopidogrel 75 mg/d	OAC: 3,371/3,371 ASA + clopidogrel: 3,335/3,335	OAC: 4,315 ASA + clopidogrel: 4,269	OAC: 158/4,315 = 3.7 ASA + clopidogrel: 159/4,269 = 3.7 RR: 0.98 (0.79–1.23)	OAC: 59/4,315 = 1.4 ASA + clopidogrel: 100/4,269 = 2.3 RR: 0.58 (0.42–0.81)	OAC: 4/4,315 = 0.1 ASA + clopidogrel: 18/4,269 = 0.4 RR: 0.22 (0.07–0.65)	OAC: 93/4,315 = 2.2 ASA + clopidogrel: 101/4,269 = 2.4 RR: 0.91 (0.69–1.21)	OAC: 21/4,315 = 0.5 ASA + clopidogrel: 11/4,269 = 0.3 RR: 1.89 (0.91–3.92)

\*See Table 2 for expansion of abbreviation.

†When person-years are not specifically reported in published studies, they are estimated in this Table based on the reported mean or median follow up times.

‡Strokes include ischemic and hemorrhagic strokes.

§Major hemorrhages include ICHs, including hemorrhagic strokes, and other major hemorrhages.

||ICHs include hemorrhagic strokes and subdural hematomas. Note: For a given study, a hemorrhagic stroke may be counted once in each of the stroke, major hemorrhage, and ICH columns.

¶Original AFASAK-1 analysis published in *Lancet*<sup>22</sup> was not intention to treat. The numbers in this table include data from the *Lancet* paper and from the 1994 pooled analysis published in *Archives of Internal Medicine*.<sup>11</sup>

#PTR-based target range: INR range is estimated.

\*\*SE counts include only SEs, although some events reported under “other vascular deaths” may have been due to SE.

††The original ESPS-2 article<sup>46</sup> does not report outcomes separately for AF patients. Data in this table are from a letter<sup>47</sup> replying to a question about the article, not from the original article. Data on AF patients are only available for stroke, not for other outcomes. Data represent rates before treatment cessation, not intention-to-treat analysis.

‡‡Annual rates for major hemorrhage are given in text, but number of events is not specified.

§§Published annual stroke rates using exact person-years are 1.1 per 100 person-years for OAC (INR 2.2–3.5) and 1.7 per 100 person-years for low dose OAC (INR 1.5–2.1).<sup>280</sup> Stroke rates for the Japanese NVAF study in this table are calculated from estimates of person-years based on mean follow up time.

|||SE events include nonfatal pulmonary or systemic emboli.

##A total of 3,410 patients were randomized; 3 withdrew before getting study medication. It was not specified to which group they were originally assigned. Only 3,407 were included for this Table.

\*\*\*Major hemorrhage rate reported in SPORTIF III<sup>30</sup> is 1.8 for major hemorrhagic events other than stroke. Major hemorrhage events reported in article are part of OT analysis, not intent-to-treat analysis.

†††Major hemorrhage events reported in SPORTIF V<sup>31</sup> as part of OT analysis, not intent-to-treat analysis.

**Table 5—Patient-Level Metaanalyses of the Efficacy of Antithrombotic Therapies in AF From Pooled Data of Randomized Trials (Section 1.1.1)**

Treatment Comparisons	RRR* (95% CI)
Adjusted-dose OAC vs no antithrombotic therapy <sup>11</sup>	68% (50–79)
Aspirin vs no antithrombotic therapy <sup>106</sup>	21% (0–38)
Adjusted-dose OAC vs ASA <sup>40</sup>	52% (37–63)

\*Outcome is ischemic stroke. Note that trials involved in each analysis are not identical.

of strokes in the warfarin arms of the trials occurred among patients who had either stopped warfarin or had an international normalized ratio (INR) or prothrombin time ratio (PTR) below the target range. In the European Atrial Fibrillation Trial (EAFT) that enrolled only patients with a transient ischemic attack (TIA) or minor stroke within the previous 3 months, the relative risk reduction was virtually identical, although the absolute risk of stroke was higher, reflecting the high risk status of EAFT patients; the annual rate of stroke in control patients was 12% vs 4% in anticoagulated patients (risk reduction 66%; 95% CI, 43 to 80%;  $p < 0.001$ ; NNT = 13).<sup>20,21</sup> In five of the studies (EAFT, the secondary prevention trial, was not included in this analysis), anticoagulation lowered the all-cause mortality rate by 33% (95% CI, 9 to 51%) and lowered the combined outcome of stroke, systemic embolism, and death by 48% (95% CI, 34 to 60%).<sup>11</sup> Overall, the evidence for the efficacy of anticoagulation in AF is strong, consistent, and based on high quality studies.

In these trials, particularly those with INR targets of 3.0 or less, anticoagulation proved adequately safe. There was no statistically significant increase in major bleeding events in patients treated with adjusted-dose anticoagulation in any of the randomized trials compared with control subjects (Table 4). The pooled analysis of the first five primary prevention trials reported an annual rate of major bleeding of 1.0% in control patients compared to 1.3% in warfarin-treated patients. These included an annual rate of intracranial hemorrhage (ICH) of 0.1% in controls compared to 0.3% in warfarin-users.<sup>11</sup>

*Description of Individual Studies:* There have been six randomized trials comparing oral anticoagulation (OAC) with no antithrombotic treatment in patients with AF.<sup>1,19,20,22–24</sup> Five were primary prevention studies in which most subjects had not had a prior stroke, TIA, or systemic embolic event and the sixth was the secondary prevention EAFT study (Tables 2–4).

These trials had notable differences in study design. First, warfarin was the oral anticoagulant used in all these trials except for EAFT which used phenprocoumon or acenocoumarol.<sup>20</sup> Second, the target intensity of anticoagulation differed. The Canadian AF (CAFA) trial, the AF, Aspirin, and Anticoagulation (AFASAK) trial, and EAFT used INR levels, with INR targets of 2.0 to 3.0, 2.8 to 4.2, and 2.5 to 4.0, respectively.<sup>19,20,22</sup> The United States-based trials used the less standardized prothrombin time ratios (PTRs): the Boston Area Anticoagulation Trial for AF (BAATAF)<sup>23</sup> and the Stroke Prevention in AF (SPINAF)<sup>24</sup> trial had a target of PTR 1.2 to 1.5, while the first Stroke Prevention in AF (SPAF I)<sup>1</sup> used PTR of 1.3 to 1.8. The INR equivalent of these PTR targets in the American trials has been roughly estimated as an INR of 1.4 to 2.8 for BAATAF and SPINAF and an INR of 2.0 to 4.5 for SPAF I (Table 2).<sup>23–25</sup> Third, SPINAF and CAFA were blinded trials while the others were open-label trials. Fourth, in BAATAF the control group was not given anticoagulation but could choose to take aspirin (46% of the patient-years in the control group were contributed by patients who were taking aspirin regularly). Finally, the definition of primary outcome and hemorrhagic outcomes varied among the trials (Tables 2, 4). All studies considered ischemic stroke a primary event, and some also included other vascular events as primary events. The definition of major bleeding varied slightly among studies. In general, bleeding was classified as major if it involved transfusion, hospitalization, or death, permanent disability, or a critical anatomic location (*eg*, intracranial). The criteria used by the BAATAF investigators were different: intracranial bleeding, fatal bleeding, or bleeding leading to transfusion of  $\geq 4$  U of blood within 48 h.

### 1.1.2 Risk of ICH During Anticoagulation

A general discussion of the hemorrhagic complications of anticoagulants is covered in the chapter by Schulman et al in this supplement. We focus on ICH in this chapter because it is the only hemorrhagic complication that regularly produces deficits as great or greater than those produced by the ischemic strokes antithrombotic therapy is designed to prevent. ICHs include both intraparenchymal hemorrhages, *ie*, hemorrhagic strokes, and nonintraparenchymal ICHs, primarily subdural bleeds. While the benefits of VKA are often balanced against the risks of aggregate major hemorrhage induced by such therapy, the preponderance of fatal or disabling hemorrhagic events on VKA are due to ICH. Ninety percent of the fatalities due to hemorrhage on VKA and nearly all persisting disability are due to intracranial, as opposed to extracranial, hemorrhage.<sup>26</sup>

Major extracranial hemorrhages, primarily GI hemorrhages, are certainly not trivial events, but their lasting impact is generally minor compared to ICHs. Overall, the rates of ICH were reassuringly low in the initial AF randomized trials comparing anticoagulation with control or placebo (Table 4). However, a substantially higher rate of ICH was observed in the SPAF II study, with seven ICHs observed among 385 patients > 75 years for an annualized rate of 1.8%, compared with 0.8% in patients on aspirin.<sup>25</sup> In contrast, in the pooled primary prevention trials the rate of ICH was only 0.3% per year among those > 75 years.<sup>27</sup> In the secondary prevention EAFT study, the average age at entry was 71 years and no ICHs were diagnosed, although a CT scan was not done in all patients with symptoms of stroke.<sup>20</sup> In the high-risk trial of SPAF III, (mean age, 71 years; mean INR, 2.4), the rate of ICH was 0.5% per year compared to a rate of 0.9% per year in the aspirin plus low-dose warfarin arm.<sup>28</sup> The AFASAK 2 study reported two ICHs in the INR 2.0 to 3.0 arm for an annual rate of 0.6%, compared to 0 to 0.3% per year rates in the three other treatment arms during a shorter period of follow-up.<sup>29</sup> In the more recent SPORTIF III and V trials, a low annual incidence of ICHs (0.2%) was observed among the 3665 patients randomized to warfarin, of whom 39% were > 75 years old.<sup>30,31</sup> Another recent trial, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-Warfarin (ACTIVE-W) study, observed somewhat more ICHs among patients randomized to oral anticoagulants compared to those taking aspirin plus clopidogrel (21 vs 11,  $p = 0.08$ ), but again, overall incidence was low (0.36 vs 0.12% per year for anticoagulants and clopidogrel/aspirin, respectively).<sup>32</sup>

The reasons for the high ICH rate in the SPAF II trial in patients > 75 years old as compared with the other studies are not entirely clear, although the patients were older than in any other AF trial, and the target anticoagulation intensity was high (INR, 2.0 to 4.5).<sup>33</sup> The importance of high INR levels in increasing the risk of VKA was further reinforced by the SPIRIT trial, a non-AF secondary stroke prevention trial which used an INR target intensity of 3.0 to 4.5.<sup>34</sup> In SPIRIT, the annual rate of ICH was > 3% among patients treated with anticoagulants. This rate was strongly related to INR values, particularly INR > 4.0.<sup>35</sup> In cohort studies of older patients anticoagulated for AF, observed rates of ICH have not been as high as in the SPAF II or SPIRIT trials.<sup>36-38</sup>

While ICHs are crucial events, they occurred at such a low rate that the individual and the aggregated AF trials observed only a small number of such events.<sup>11</sup> As a consequence, these randomized trials have not been a rich source of information on the

determinants of ICH. By contrast, large observational studies can accumulate informative numbers of ICHs on anticoagulation. These studies reveal a dramatic increase in the risk of ICH at INR values > 4.0, though most ICHs among patients treated with anticoagulants occur at INR values < 4.0. In addition, the risk of ICH appears to rise with patient age and in those with prior ischemic stroke.<sup>39</sup>

### 1.1.3 Efficacy of Aspirin vs Placebo

*Results of Systematic Reviews of Aspirin vs No Aspirin:* In contrast to the consistent evidence demonstrating the marked efficacy of VKA therapy in preventing stroke in AF, the trials of aspirin suggest little, if any, such efficacy. Five older and two more recent studies, described below, compared aspirin with control. An individual patient-level metaanalysis pooling data from the AFASAK 1, SPAF I, and EAFT trials resulted in an estimated relative risk reduction of 21% compared to placebo.<sup>40</sup> The associated confidence interval ranged from 0 to 38% RRR, indicating results at the cusp of statistical significance (Table 5). This metaanalysis did not account for the marked heterogeneity of effect of aspirin seen in the two component trials of SPAF I (discussed below). Accounting for such heterogeneity would have resulted in the lower bound of the confidence interval extending well into the negative range of efficacy.

In addition to the pooled patient-level analysis described above, there have been other study-level metaanalyses of aspirin vs control in patients with AF. The first found a 22% (95% CI, 2 to 38%) reduction in the risk of stroke.<sup>41</sup> This has been updated recently.<sup>42</sup> A second metaanalysis concluded that aspirin results were heterogeneous because of disparate results in the two cohorts of the SPAF I trial. The random effects analysis employed produced a similar point estimate but much wider confidence intervals: RRR = 24% (- 33% to + 66%).<sup>43</sup>

*Description of Individual Studies:* Four trials were placebo-controlled, and three studies had a nontreatment control. The dose of aspirin varied between 50 and 325 mg/d. Three of the original trials of OAC with VKAs included aspirin arms, AFASAK 1 (75 mg/d),<sup>22</sup> SPAF I (325 mg/d),<sup>1</sup> and EAFT (300 mg/d).<sup>20</sup> Aspirin was not statistically significantly more effective than placebo in AFASAK 1 and EAFT. Evidence of aspirin efficacy comes mainly from the SPAF I trial, in which a statistically significant 42% relative risk reduction was reported. SPAF I was composed of two separately randomized cohorts, one consisting of individuals

who could not be randomized to warfarin (aspirin vs placebo) and one for individuals who could be randomized to warfarin (in this trial there was also a warfarin arm). In the first cohort, the relative risk reduction afforded by aspirin was a highly significant 94%, while in the second cohort the comparable relative risk reduction was an insignificant 8%, similar in magnitude to the effect found in AFASAK 1 and EAFT.<sup>44</sup> The LASAF study reported inconsistent effects of aspirin in its two component trials (125 mg/d vs control and 125 mg every other day vs control).<sup>45</sup> Data from other trials also bear on the efficacy of aspirin. ESPS-2 (European Stroke Prevention Study) was a large trial that included a comparison of 50 mg/d of aspirin vs placebo to prevent stroke recurrence, primarily involving non-AF patients. A subset analysis of its AF patients published in a letter to the editor reported a nonsignificant 33% relative risk reduction vs placebo.<sup>46,47</sup> The BAATAF trial also reported a nonrandomized comparison of patients in its control arm who took aspirin with those who did not, reporting no efficacy of aspirin in this low-powered analysis.<sup>48</sup>

A Japanese trial randomized patients to aspirin (150 to 200 mg/d) vs a control group.<sup>49</sup> This study was stopped prematurely due to an interim analysis showing that aspirin was associated with a slightly higher risk of major bleeding (1.6% vs 0.4%,  $p = 0.10$ ) and was unlikely to be superior to control in terms of primary end points. This study raised concerns that the risk of ICH might be greater in patients of Asian ethnicity. A study conducted in Sweden compared aspirin at 75 mg/d combined with low-dose OAC to a nontreatment control among intermediate risk patients with AF.<sup>50</sup> There was no statistically significant difference in stroke rates in the two treatment arms but there was a significantly increased rate of bleeding in the aspirin plus low-dose OAC arm. The study was underpowered since it did not reach its recruitment goal.

#### 1.1.4 Efficacy of Oral Anticoagulant Therapy vs Aspirin

*Systematic Reviews of Randomized Trials of Warfarin vs Aspirin:* Seven studies compared oral VKAs directly with aspirin (Table 2). Overall, these results suggest that the risk reduction associated with oral VKA therapy is much greater than that provided by aspirin. A metaanalysis of these studies reported a 36% (95% CI, 14 to 52%) relative reduction in the risk of all stroke with adjusted-dose OAC compared with aspirin, and a 46% (95% CI, 27 to 60%) reduction in the risk of ischemic stroke.<sup>41</sup> The

difference between the two analyses was largely due to the increased rate of intracerebral hemorrhage in the SPAF II study where the target INR range (INR, 2.0 to 4.5) extended well above currently recommended intensities.<sup>25</sup> Probably the highest quality assessment of currently available data was the patient-level metaanalysis from the AFASAK 1 and 2, EAFT, PATAF, and SPAF II and III studies, which found a RRR of 46% (95% CI, 29 to 57%) for all stroke and 52% (95% CI, 37 to 63%) for ischemic stroke with VKAs compared to aspirin (Table 5).<sup>40</sup> Major hemorrhage was increased 1.7-fold (95% CI for hazard ratio, 1.21 to 2.41). On balance, treating 1000 patients with AF for 1 year with adjusted-dose oral anticoagulants rather than aspirin (ASA) would avoid 23 ischemic strokes while causing 9 additional major bleeds. The SPAF III and AFASAK 2 trial results were included in both this pooled analysis and the previously cited metaanalysis, even though patients in the aspirin arms were also treated with very small doses of warfarin, based on the conclusion that such low-dose warfarin had no effect.

VKA therapy targeted at INR 2.0 to 3.0 was tested against aspirin in two recently completed trials enrolling elderly patients with AF. The small WASPO trial randomized 75 patients aged 80 to 90 years to warfarin or aspirin, 300 mg/d, and found that warfarin was superior to aspirin, with a higher rate of side effects and intolerability among patients in the aspirin arm.<sup>51</sup> In the much larger and more definitive BAFTA study, AF patients, age 75 years and older, were also randomized to receive warfarin, target INR 2.0 to 3.0, or aspirin, 75 mg/d. In BAFTA the relative risk reduction for all disabling or fatal stroke favoring warfarin was 48% and there was no increase in major bleeding.<sup>52</sup>

The results of these studies were further confirmed by the ACTIVE-W trial which tested VKAs targeted at INR 2.0 to 3.0 vs the combination of aspirin plus clopidogrel in higher risk AF patients (discussed below) as well as a trial comparing aspirin to warfarin in China.<sup>32,53</sup> ACTIVE-W found that VKAs reduced the risk of ischemic stroke by 53% compared with aspirin plus clopidogrel. In summary, the weight of evidence shows that aspirin has little effect in preventing stroke in AF and is markedly inferior to VKA therapy, with a consistent RRR of about 50% favoring adjusted-dose warfarin.

*Description of Individual Studies:* SPAF II included two separate trials, one for individuals  $\leq 75$  years old and one for those  $> 75$  years old (Table 3).<sup>25</sup> In the younger group (mean age, 65 years), adjusted-dose warfarin decreased the rate of stroke by 33%, compared with a 27% reduction in the older patients (mean age, 80 years); neither difference was

statistically significant. SPAF II included the experience of patients who had participated in the group 1 trial in SPAF I, in which aspirin-treated patients had an extremely low event rate.<sup>1,44</sup> SPAF I, group 2 patients, among whom aspirin was ineffective, could not be rolled over into SPAF II because group 2 patients were deemed to be poor warfarin candidates. This design feature biased the trial's results in favor of aspirin. In addition, many of the strokes in the warfarin arm of SPAF II occurred in individuals who had stopped warfarin.

In the SPAF III high-risk trial, AF patients who had at least one of four thromboembolic risk factors (recent congestive heart failure or left ventricular fractional shortening < 25%; history of a thromboembolism; systolic BP > 160 mm Hg at study entry; or a woman > 75 years) were randomly assigned to either a combination of low-intensity, fixed-dose warfarin (INR, 1.2 to 1.5; daily dose of warfarin,  $\leq$  3 mg) plus aspirin (325 mg/d), or adjusted-dose warfarin (target INR, 2.0 to 3.0). AFASAK 2 randomized patients to warfarin 1.25 mg daily and aspirin (300 mg/d), or adjusted dose warfarin (target INR, 2.0 to 3.0).<sup>28</sup>

In AFASAK 1 and EAFT, adjusted-dose warfarin decreased the risk of primary events by 48% and 40%, respectively, compared with aspirin (300 mg/d) (both results were statistically significant).<sup>20,22</sup> The SPAF III high-risk study found a marked superiority of adjusted-dose warfarin (INR, 2.0 to 3.0) over low-dose warfarin plus aspirin, RRR = 74%. AFASAK 2 was a study of moderate risk patients (excluded were patients < 60 years old with lone AF and those with a history of stroke/TIA in the past 6 months or BP > 180/100 mm Hg).<sup>54</sup> The trial was stopped about midway through the planned enrollment, in part because of the results of SPAF III. As a result, it did not have substantial power to detect a difference between the two treatment regimens. The annual risk of primary events was not significantly different between the group receiving adjusted-dose warfarin (3.4%) and those receiving the aspirin-warfarin combination (2.7%). The PATAF Dutch general practice physicians study reported a 22% relative reduction in the risk of the primary outcome cluster with full dose oral VKA therapy compared to aspirin, 150 mg/d, but this was not statistically significant; low event rates limited the power of this comparison (Tables 3, 4).<sup>55</sup> Finally, a recent trial conducted in China found that warfarin reduced the risk of ischemic stroke by 62% compared to aspirin and reduced the combined outcome of ischemic stroke plus death by 56% ( $p = 0.03$ ).<sup>53</sup>

In WASPO only 75 patients were randomized, 36 to warfarin. As a result, the study was underpowered

to assess outcomes (no strokes were observed during the very limited aggregate person-years of follow-up).<sup>51</sup> Three serious bleeding events were observed, all in the aspirin arm. BAFTA was a definitive test of aspirin, 75 mg/d, vs warfarin, INR 2.0 to 3.0, with 485 patients randomly assigned to aspirin and 488 to warfarin. Follow-up averaged 3 years. The outcome event was all disabling or fatal stroke, systemic embolus, and ICH. The rate of such events was 3.8% per year in the aspirin arm vs 1.8% per year in the warfarin arm ( $p = 0.0027$ , intention-to-treat). There was no increase in major bleeding with warfarin, including no increase in ICH.<sup>52</sup> These results among elderly patients with AF were essentially the same as those of trials with a younger distribution of patients. They are particularly reassuring that older patients with AF do not face additional risk of major bleeding attributable to VKA therapy.

### 1.1.5 Effects on Stroke Severity

While analyses have emphasized the relative efficacy of antithrombotic agents in reducing the risk of all ischemic stroke, it appears that oral VKA therapy has the important specific advantage of preventing severe strokes. This effect was observed in the SPAF studies and ascribed to better prevention of cardioembolic strokes.<sup>56,57</sup> Metaanalyses indicate that aspirin's efficacy compared to placebo diminishes from 22% for all stroke to 13% ( $-19\%$  to  $36\%$ ) for disabling stroke (even without accounting for the heterogeneity of effect seen in SPAF I).<sup>41</sup> By contrast, adjusted-dose warfarin is just as efficacious in preventing disabling stroke as stroke events of lesser severity. The pooled analysis comparing adjusted-dose oral VKA therapy to aspirin observed that such anticoagulants significantly decreased the annual rate of fatal ischemic strokes (0.5 vs 0.2 events per 100 person-years, respectively;  $p = 0.01$ ).<sup>40</sup> Recent analysis of a large cohort study indicates that anticoagulation at INR  $\geq$  2.0 is associated with far better short-term survival should stroke occur.<sup>58</sup> Stroke in patients with AF is generally more severe than stroke in patients without AF, probably reflecting a greater proportion of embolic events.<sup>59</sup> The available evidence indicates that full adjusted-dose oral VKA therapy (INR  $\geq$  2.0) effectively prevents such severe strokes in AF.

### 1.1.6 Oral Anticoagulation vs Other Antiplatelet Regimens

In a randomized trial comparing adjusted-dose warfarin with the platelet inhibitor indobufen, there was no significant difference in the incidence of the combined end point of stroke, myocardial infarction, pulmonary embolism, or vascular death between the

two groups (12% in indobufen group vs 10% in warfarin group;  $p = 0.47$ ).<sup>60</sup> There were four major GI hemorrhages in the warfarin group and none in the indobufen group. The frequency of major bleeding episodes was 0.9% in the warfarin group and 0% in the indobufen group (Tables 3, 4). Another trial (ACTIVE-W) compared 6706 patients eligible for OAC to either a combination of clopidogrel (75 mg/d) plus aspirin (75 to 100 mg/d) or adjusted-dose warfarin. Of note, most subjects (77%) were taking oral anticoagulants prior to the trial. The study was stopped prematurely when an interim analysis demonstrated that clopidogrel plus aspirin was associated with higher event rates (RR of 1.44 [1.18–1.76]). Although rates of major hemorrhage were similar in the two groups, the rate of ICH was somewhat higher in the OAC arm (Tables 3, 4). Higher rates of discontinuing warfarin and worse INR control were noted in patients who had not been on oral anticoagulants prior to the study, factors that may have contributed to the observation that warfarin appeared less beneficial in this subgroup (RR 1.27 [0.85–1.89]).<sup>32</sup>

### 1.1.7 Trials Comparing Standard vs Low-Dose Anticoagulation

Several studies assessed very low INR intensities and/or fixed low doses of anticoagulants in an attempt to reduce the risk of bleeding and the burden inherent in adjusted-dose anticoagulation (Table 2).<sup>28,50,54,55</sup> Very low intensity/low dose anticoagulation proved unsuccessful. In a previous section we included the SPAF III and AFASAK 2 trials as tests of aspirin vs warfarin targeted at INR 2.0 to 3.0. In these trials, aspirin was coupled with low doses of warfarin such that the INR increased minimally. The SPAF III randomized trial, which enrolled patients at high risk for stroke, was terminated early because of a substantially increased rate of primary outcome events in patients taking combination therapy with fixed-dose, low-intensity warfarin (maximum daily dose of 3 mg targeting INR 1.2 to 1.5) plus aspirin 325 mg/d.<sup>28</sup> The event rate was 7.9% per year among those randomly assigned to combination therapy vs 1.9% per year among those randomized to adjusted-dose warfarin with a target INR of 2.0 to 3.0. The absolute difference in stroke rate of 6% per year translates into a NNT of 17. The high stroke rate in the combination therapy arm of this trial and the relative risk reduction of 74% conferred by adjusted-dose warfarin suggest that the low-intensity anticoagulation selected for this study was ineffective in these high-risk AF patients. No evidence of a positive synergistic effect of the low-dose warfarin-aspirin combination could be detected. No signifi-

cant differences in the rates of major hemorrhage were detected between the two groups (Tables 3, 4).

In the section on the efficacy of aspirin vs warfarin, above, we reviewed the results of the AFASAK 2 comparison of adjusted-dose warfarin (INR, 2.0 to 3.0) vs fixed-dose warfarin at 1.25 mg/d plus aspirin at 300 mg/d.<sup>54</sup> In essence, these statistically insignificant results were indeterminate.

PATAF, AFASAK 2, and the trial of Pengo et al also compared low-dose warfarin (1.25 mg daily) vs adjusted-dose warfarin, INR 2.0 to 3.0. In PATAF, the risk of stroke was slightly lower in patients randomized to a target INR of 1.1 to 1.6 compared with OAC with a target INR of 2.5 to 3.5 (risk reduction 14%).<sup>55</sup> In the latter two studies, the risk of stroke was reduced by 13% and 42% in the adjusted-dose anticoagulation groups (not statistically significant).<sup>54,61</sup> The Swedish SAFT study randomized patients at intermediate stroke risk (ie, estimated between 0.5% and 4% per year) to fixed low-dose warfarin at 1.25 mg/d plus aspirin 75 mg/d vs control (no antithrombotic therapy). Although there were fewer strokes in the warfarin/aspirin group than in the control group (hazard ratio, 0.78 [0.49–1.23]), the comparison was not statistically significant.<sup>50</sup>

A metaanalysis combining the results of the three trials comparing low-dose to adjusted-dose warfarin yielded a relative risk reduction of 38% (95% CI, 20 to 68%) in favor of adjusted dose OAC.<sup>41</sup> Taken with the impressive results of SPAF III, it is clear that anticoagulation using VKA therapy targeted at INR levels of 1.5 or less is ineffective.

### 1.1.8 Trials Assessing a VKA Combined With an Antiplatelet Agent

Trials testing combinations of oral anticoagulants plus antiplatelet agents are motivated by several goals including reducing hemorrhage risk by using lower INR targets while retaining efficacy, and adding further stroke-preventive efficacy to usual INR targets for particularly high-risk groups. This latter strategy has reduced embolic event rates in patients with mechanical heart valves.<sup>62</sup> A third goal of combination therapy is to add protection against coronary artery disease to stroke-preventive protection among patients with AF who are at particularly high risk for future coronary disease, such as those who have known coronary artery disease or diabetes. We reported in the prior section on two trials, SPAF III and AFASAK 2, that combined very low intensities of anticoagulation with aspirin. The regimens used in these trials were not effective in preventing strokes (Tables 3, 4).<sup>28,54</sup>

Two trials in AF used substantially higher intensi-

ties of anticoagulation combined with anti-platelet agents. The French Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontane (FFAACs) study, compared the oral anticoagulant fluindione, INR target 2.0 to 2.6, alone or combined with aspirin, 100 mg/d, vs fluindione alone, INR target 2.0 to 2.6.<sup>63</sup> Enrolled patients were at high risk of ischemic stroke using SPAF III criteria. The trial was stopped early because of excessive hemorrhage in the group receiving fluindione plus aspirin. At trial termination, only 157 patients had been entered and mean follow-up was only 0.84 years.

In the much larger NASPEAF study (Tables 2–4) patients were stratified into a higher-risk group (n = 495) with AF and rheumatic mitral stenosis or AF and a history of embolism, and a lower-risk group (n = 714) with AF and age > 60 years, hypertension or heart failure.<sup>17,64</sup> The higher-risk patients were randomly assigned to treatment with anticoagulation with oral VKA therapy using a target INR of 1.4 to 2.4 combined with the platelet cyclooxygenase inhibitor triflusal (600 mg daily, approximately equivalent to 300 mg of aspirin) or anticoagulation (INR, 2 to 3) alone. The lower-risk patients were randomly assigned to triflusal alone, anticoagulation to an INR of 2.0 to 3.0, or the combination of triflusal plus anticoagulation to an INR of 1.25 to 2.0. The group receiving combination therapy had a significantly lower risk of primary outcome events (thromboembolism plus cardiovascular death) than the group treated with anticoagulants alone, in both risk groups. In the lower-risk trial, both of the groups receiving anticoagulants did significantly better than those receiving triflusal alone (Tables 3, 4). There were substantially more heart failure and sudden deaths in the group receiving anticoagulants alone than in the combination arms. As a result, the difference between combination therapy and anticoagulation alone was less striking when the outcome was restricted to ischemic stroke, other thromboembolism, and TIA. Rates of severe bleeding, including ICH, were lower in the combination therapy arm than in the anticoagulants alone arm, but this difference was not statistically significant. Of note, the levels of anticoagulation actually achieved in the anticoagulation and combination arms were closer than planned (mean INR of 2.5 for anticoagulation alone in both risk strata vs mean INR of 1.96 and 2.18 for the combination arms in the lower and higher-risk strata, respectively). The NASPEAF investigators concluded that combination therapy was superior to anticoagulation alone in both strata. This conclusion is made less definitive by the fact that the differences in primary outcome resulted largely from outcomes that probably were not due to thromboembolism and that the achieved INR levels were

similar in the anticoagulation and combination groups. Nonetheless, these results certainly suggest that combination therapy can be effective if targeted INR levels are closer to the standard range and may add a degree of safety.

### *1.1.9 Addition of Aspirin to VKAs To Reduce Risk of Coronary Heart Disease*

Roughly a third of patients with AF also carry a diagnosis of coronary artery disease. These patients face a sizable risk of future coronary events as well as stroke. For such individuals who are receiving anticoagulants to prevent stroke, should aspirin be added to better prevent coronary events? There are no randomized trials that directly address this issue by comparing VKAs (INR, 2.0 to 3.0) to VKAs (INR, 2.0 to 3.0) plus a daily aspirin in patients with both AF and coronary artery disease. We must base our assessment on trials in related subgroups of patients.

Anticoagulants have been tested in patients with coronary artery disease, most of whom do not have AF. These trials demonstrate that anticoagulation alone using INR targets higher than that for AF (*eg*, INR, 2.8 to 4.8) can substantially reduce the risk of recurrent coronary events.<sup>65</sup> Subsequent trials have demonstrated that addition of aspirin (75 to 100 mg/d) to OAC using lower INR targets (*eg*, INR, 2.0 to 2.5) may add a small measure of efficacy with increased minor bleeding.<sup>66,67</sup> Patients in these coronary artery disease trials were, on average, about 10 years younger than patients with AF, raising the concern that the results (particularly the hemorrhage results) may not fully generalize to patients with AF. Clinical trials to prevent stroke in AF also provide relevant information. In particular, the patient-level metaanalysis of AF trials comparing aspirin to OAC observed that OAC alone prevented CAD, as well as ischemic stroke, better than aspirin alone.<sup>40</sup> From these data, one can infer that OAC alone targeted at an INR of 2.0 to 3.0 can provide substantial protection against recurrent coronary disease. There is a cost to adding aspirin to OAC. In secondary, non-randomized analyses from the AFFIRM and SPORTIF trials, addition of ASA to OAC was associated with a doubling of bleeding risk after controlling for other significant risk factors for major bleeding.<sup>68–70</sup> While addition of aspirin may provide some further protection against coronary disease it poses an additional risk of hemorrhage. There is also no clear evidence that addition of ASA to OAC adds further protection against ischemic stroke in AF patients.<sup>69</sup> [further discussion of the use of antithrombotic agents in coronary artery disease can be found in the chapter by Becker et al in this supplement.]

### 1.1.10 Anticoagulation in Patients With AF Undergoing Percutaneous Coronary Intervention and Stenting

This topic is addressed in the chapter by Becker et al and assessment of bleeding risk is addressed in the chapter by Schulman et al in this supplement. AF and treatment of coronary disease with PCI and stenting are both common with the result that increasing numbers of patients with AF are treated with PCI. The clinician then faces the question of whether to treat with full antiplatelet therapy to forestall coronary events plus anticoagulation with VKA to prevent AF-related stroke, in the process raising risk of bleeding complications. A recent metaanalysis with estimates of risk and benefit of warfarin plus aspirin after myocardial infarction or acute coronary syndromes concluded that for patients who are at low or intermediate risk for bleeding, the cardiovascular benefits of warfarin outweighed the bleeding risks.<sup>71</sup> However, patients with AF tend to be considerably older than those included in usual studies of acute coronary disease. Recent large trials in AF have demonstrated a doubling of hemorrhage risk among patients taking aspirin in addition to warfarin.<sup>68,69</sup> With PCI and stenting in patients with AF, we face the additional risk of thienopyridine derivatives (clopidogrel or ticlopidine) plus aspirin added to VKA therapy. The ACTIVE-W trial demonstrated that clopidogrel plus aspirin is not highly protective against ischemic stroke in patients with AF.<sup>32</sup> While VKA therapy might be held for a few weeks following PCI, longer periods off VKAs will incur significant risks of stroke. Thienopyridine derivatives plus aspirin are now prescribed for long periods with drug-eluting stents. At this point, there is little evidence bearing on the balance of risks of combining or keeping separate the intense antiplatelet regimen needed for PCI and stents and VKA therapy for AF.<sup>72,73</sup>

### 1.1.11 Other Anticoagulant Agents

While clearly efficacious against stroke in patients with AF, the narrow therapeutic margin of oral VKAs and their interactions with numerous drugs and foods require frequent and bothersome INR testing and dose adjustments. VKAs are hardly ideal therapeutic agents. The large and increasing number of individuals with AF and improved ability to specifically interrupt thrombogenesis has prompted productive development of alternative antithrombotic agents. However, to this point, trials of novel antithrombotic agents have been notably unsuccessful and have further supported the remarkable efficacy and relative safety of VKA therapy in the controlled environment of randomized clinical trials. Ximel-

agatran, an oral direct thrombin inhibitor, was tested in the SPORTIF trials and found to have near-equivalent efficacy and safety as VKA therapy but was withdrawn because of rare fatal liver toxicity.<sup>30,31,74,75</sup> Idraparinux, an injectable indirect factor X inhibitor, was tested in the AMADEUS trial. AMADEUS was stopped early in favor of VKA therapy. At the time of this writing the details of the AMADEUS trial have not been published. Finally, aspirin plus clopidogrel, was tested against VKA therapy in the ACTIVE-W trial which was also stopped early because VKA therapy was much more efficacious and as safe as the combined antiplatelet approach.<sup>32</sup> More detailed description of these trials is provided below. Multiple other novel agents are in development with several in, or about to start, pivotal phase III trials.<sup>76–78</sup> While VKA therapy remains risky and bothersome, it has proved remarkably difficult to displace.

Because VKA therapy is now the established effective treatment for individuals with AF at elevated risk for ischemic stroke, alternative therapies must be tested directly against VKA therapy, as opposed to tested against placebo. Because of VKAs' extraordinary efficacy, no manufacturer has chosen to test the superiority of their novel antithrombotic agent over VKAs. To date, all have used "noninferiority" trial designs. The starting hypothesis for such trials is that VKAs are superior to the novel agent. The trial is then powered to reject this hypothesis such that the upper bound of the confidence interval of the effect measure (*eg*, risk difference or risk ratio) excludes the posited level of superiority. This posited level of superiority is a crucial design element. If it is too large, agents that are truly inferior by an important margin may be declared noninferior. Indeed, agents with no intrinsic efficacy may be declared noninferior. However, as the posited margin of superiority is decreased, the required sample sizes increase rapidly and the cost of the trial becomes onerous. The SPORTIF trials used a superiority margin of an absolute risk difference of 2% per year. The FDA review of the ximelagatran application criticized this margin as being too large.<sup>74,75,79,80</sup> Subsequent noninferiority trials vs. VKAs in AF have used even smaller superiority margins necessitating enrollment of many thousands of patients, dwarfing the size and costs of the original, highly informative trials of VKA vs placebo.<sup>76–78</sup>

These recent noninferiority trials vs VKA in AF have also faced troublesome challenges to generalizability. Prevalent, stable users of VKA therapy have been preferentially enrolled in these trials.<sup>30–32</sup> Further, a crucial element underpinning the validity of noninferiority designs is that the traditional therapy must be managed in a high quality fashion. Partly as

a consequence of preferential recruitment of stable users of VKAs and of trial-level, high-quality management of VKAs, the performance of VKA therapy in recent trials has been extraordinarily good with very low rates of strokes and major bleeds. The concern is that the trials provide an unrealistically favorable record of the performance of VKAs. Such concerns highlight the importance of tracking the performance of VKAs in usual clinical care.<sup>81</sup>

*Description of Individual Studies: Ximelagatran:* Ximelagatran is an orally administered prodrug converted after absorption to melagatran, an active direct thrombin inhibitor.<sup>82</sup> Because the compound displayed stable pharmacokinetics independent of the hepatic P450 enzyme system, and a low potential for food<sup>83</sup> or drug<sup>84</sup> interactions, it could be administered in a fixed dose without coagulation monitoring. Ximelagatran compared favorably with both low-molecular-weight heparin (LMWH) and adjusted-dose warfarin for prevention of venous thromboembolism<sup>84–88</sup> and with warfarin for treatment of established deep vein thrombosis (DVT).<sup>83</sup>

Two large, long-term phase III noninferiority studies compared ximelagatran, 36 mg bid, with warfarin (INR, 2.0 to 3.0) in patients with AF and at least one risk factor for stroke: Stroke Prevention using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Atrial Fibrillation (SPORTIF III) and SPORTIF V (Tables 2–4).<sup>89</sup>

Among warfarin-assigned patients, INR values fell within the intended therapeutic range for 66% of the duration of exposure in SPORTIF III<sup>30</sup> and 68% in SPORTIF V,<sup>31</sup> and the mean INR was 2.5 across all measurements.<sup>70</sup> In SPORTIF III<sup>30</sup> 56 primary events occurred in the warfarin group, an annual rate of 2.3%, and 40 occurred in the ximelagatran group, 1.6%/year (not significantly different). In SPORTIF V,<sup>31</sup> there were 37 events in the warfarin group (1.2%/year), and 51 events in the ximelagatran group (1.6%/year; absolute difference, 0.45% per year; 95% CI, 0.13 to 1.03% per year) and there was no difference between treatment groups in rates of major bleeding.<sup>31</sup>

The primary analysis of each trial supported the assertion of noninferiority using the absolute margin of 2% per year. A prespecified pooled analysis showed that the number of outcome events in both arms was almost identical: 93 primary outcome events in patients assigned to warfarin and 91 among those assigned to ximelagatran (rate difference,  $-0.03\%$ /year; 95% CI,  $-0.50$  to  $0.44\%$ /year).<sup>70</sup> There was no significant difference between treatments in rates of hemorrhagic stroke, fatal bleeding, or other major bleeding.

In both the SPORTIF III and V trials, serum

alanine aminotransferase levels rose to  $> 3$  times the upper limit of normal in about 6% of patients treated with ximelagatran.<sup>70</sup> Most importantly, there were several additional deaths in the ximelagatran arms resulting from liver failure.<sup>75,80,90</sup> In part because of concerns about liver toxicity, ximelagatran was not approved by the FDA for use in the United States. The manufacturer subsequently withdrew the drug worldwide after an additional case of severe liver injury was observed to occur rapidly after a short course of ximelagatran in a clinical trial in orthopedic surgery.<sup>91</sup>

The ximelagatran experience demonstrated that a fixed dose novel anticoagulant can have antithrombotic efficacy and bleeding risk comparable to tightly controlled warfarin therapy. Other molecular forms of synthetic oral direct antithrombin agents are in development. In particular, dabigatran is being tested in a large phase 3 trial among individuals with AF.<sup>76</sup> Molecules aimed at other targets are also under development for this indication. Evaluation of each will require large trials because the active comparator (*eg*, warfarin) will necessarily be highly effective, resulting in low event rates.

*Idraparinix:* Idraparinux is a once-weekly, fixed dose, injectable, indirect factor X inhibitor. It was tested against adjusted-dose VKA therapy, INR target 2.0–3.0, in a large phase 3 randomized trial of patients with AF and at least one risk factor for stroke, the AMADEUS trial. At an early interim analysis, the trial was stopped in favor of VKA therapy. No further details of this trial have been made public at the time of this writing.

#### 1.1.12 Effectiveness of Antithrombotic Therapy for AF in Clinical Practice

Despite the extensive data from randomized trials demonstrating the efficacy of adjusted-dose warfarin for prevention of thromboembolism, concerns persist about how generalizable these findings are when applied to “real world” clinical practice settings. The trials enrolled only a small proportion of screened patients (*eg*,  $< 10\%$  in SPAF), relatively few very elderly patients (only 10% were  $> 80$  years old), and they used especially careful and frequent monitoring of anticoagulation intensity.<sup>1,11</sup> Further, recent trials have preferentially enrolled patients who were experienced, and presumably stable, users of VKAs.<sup>30–32</sup>

Studies of the outcomes of antithrombotic therapy in patients with AF in nontrial clinical settings have often involved hospitalized patients or other selected populations (*eg*, patients in nursing homes), were limited by relatively small patient samples, and accumulated relatively few thromboembolic and hem-

orrhagic outcome events leading to imprecise estimates of event rates.<sup>92–98</sup> Among survivors of ischemic stroke with AF, warfarin was more effective than aspirin for reducing recurrent stroke, and recurrent stroke rates were lower during periods on vs off warfarin.<sup>99,100</sup> In two studies of hospitalized patients with nonvalvular AF, the risk of stroke or transient ischemic attack was lower in patients discharged on warfarin than in those given no antithrombotic therapy (adjusted relative risks 0.76 and 0.31) and thromboembolic rates were lower with warfarin than aspirin.<sup>93,95</sup> In selected cohorts of patients with AF treated with anticoagulation, the risk of stroke varied from 1.3% annually to 2.0 per 100 person-years.<sup>97,98</sup> In a large study from Denmark involving 5124 persons with AF based on hospital discharge or outpatient diagnoses between 1991 and 1998, investigators observed stroke rates of 3% per year overall, with a protective effect of warfarin in men (adjusted relative risk, 0.6; 95% CI, 0.4 to 1.0) but not in women.<sup>101</sup> In these observational studies, annual rates of ICH on anticoagulation were relatively low (range, 0 to 0.8%) and comparable to rates in prior randomized trials, although confidence limits were wide.<sup>92,94,98,100</sup> More recent studies from Italy, England, and United States Medicare populations all find reduced rates of stroke among AF patients treated with VKAs.<sup>8,102–104</sup> As with most studies of the effect of antithrombotic therapy for AF in usual clinical care, these studies used database coding of outcome events without clinical validation and inferred use of warfarin through indirect methods (eg, via coding for INR tests). Similarly, assembly of AF patients was typically based on International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes without validation and several studies assembled their cohorts from hospitalized patients. These methodologic limitations probably bias the estimates of VKA effectiveness to the null and may also identify patients with somewhat higher risk of stroke than the typical AF patient.

The AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study assembled a community-based cohort of 13,559 ambulatory adults with nonvalvular AF diagnosed in the outpatient setting.<sup>81</sup> Use of warfarin was established by prescription records and INR testing and test results. All ICD-9 identified events were validated by clinical record review. During the first follow-up of the entire cohort 598 validated thromboembolic events were observed and the rate of thromboembolism was significantly less on adjusted-dose warfarin compared to no warfarin therapy (including aspirin and no antithrombotic therapy): (1.36% vs 2.53% per year, respectively,  $p < 0.001$ ), with a 49% (95% CI,

39 to 57%) adjusted risk reduction. Intracranial hemorrhage rates were low on or off warfarin (0.51% vs 0.33% per year, respectively), although warfarin was associated with an increased risk of ICH (adjusted RR, 1.57; 95% CI, 1.10 to 2.26). In the subgroup of 11,526 cohort members without potential contraindications to anticoagulation at study entry, use of adjusted-dose warfarin was associated with a 51% (95% CI, 39 to 60%) lower adjusted risk of thromboembolism and a moderately increased risk of ICH (0.46% vs 0.23% per year, respectively,  $p = 0.003$ ) compared with no warfarin therapy. ATRIA patients on warfarin were predominantly managed by dedicated anticoagulation units and INR time-in-range was  $> 60\%$ . Such INR control is not far below figures reported for recent randomized trials (eg, SPORTIF<sup>31</sup> and ACTIVE<sup>32</sup>) although extended gaps in testing were probably greater. Similar quality of INR control has been reported for other AF cohorts.<sup>105</sup>

Overall, existing data indicate significant effectiveness and relative safety of oral VKAs in patients with AF treated in clinical practice as long as high quality management of anticoagulation is maintained. Additional studies of the oldest patients with AF are needed, however, since these individuals face the highest risk of both stroke and hemorrhagic complications and were not well represented in prior randomized trials. Cohorts enriched with patients initiating VKA therapy are needed to give more precise assessments of bleeding risks during this particularly vulnerable period.

### 1.1.13 Risk Stratification in Patients With AF

Oral VKA therapy is very effective in decreasing the risk of ischemic stroke in patients with AF.<sup>11,41,43,106</sup> In trials enrolling average risk patients without a history of recent stroke or with no history of stroke (“primary prevention” patients),<sup>11</sup> in trials with very high risk patients with a relatively recent history of stroke (“secondary prevention” patients),<sup>20</sup> and in trials with increased risk patients having a mix of qualifying risk factors,<sup>28</sup> adjusted-dose VKA therapy consistently proved extremely effective at preventing ischemic stroke and was adequately safe. Indeed, there is no specific subset of AF patients where VKAs have been shown to be inferior to any comparator. A reasonable interpretation of this large set of trials would be to recommend VKA therapy for all patients with AF. This conclusion should be kept in mind as we discuss the alternative “risk-based” approach to selecting AF patients for VKA therapy currently favored by published guidelines.

Guidelines have recommended that use of VKA therapy in AF be based on the patient’s risk of ischemic stroke off VKA therapy; the higher this risk the stronger the indication for VKAs.<sup>107,108</sup> These

recommendations target use of VKAs in AF because such anticoagulants raise the risk of major hemorrhage and because necessary INR monitoring and dose-adjustment make VKA therapy burdensome. The goal of risk-based approaches is to avoid the use of VKAs in patients at such low risk of stroke, untreated, that toxicity may outweigh benefit, and to urge the use of VKAs in patients at high enough risk of stroke that use of VKAs has a clear expected net health benefit. Such recommendations assume that VKA therapy's relative risk reduction for stroke remains constant across patient subgroups, an assumption that has not been explicitly tested but is supported by trial results.<sup>11,20,28</sup> Guidelines generally pose the risk-based therapeutic decisions as VKAs vs aspirin. However, it should be clear that the core decision is VKAs, yes or no. Aspirin is typically used when the decision is "no VKA" because of a hopeful rather than critical assessment of the evidence bearing on aspirin and because aspirin may safely afford some protection against other vascular disease, in particular, coronary disease. While guidelines are explicit about risk factors for ischemic stroke in AF they tend to be vague about risk of hemorrhage with VKAs, leaving the assessment of this latter risk up to the managing physician. Variation in guideline recommendations for antithrombotic therapy for AF results from differences in risk stratification for ischemic stroke.<sup>109,110</sup> These differences, in turn, result from modest differences in assessing stroke risk and larger differences in setting stroke risk thresholds for use of VKAs.<sup>110–112</sup> The current section of this chapter focuses on evidence informing risk stratification for stroke based primarily on randomized trials and large observational studies, while the chapter by Schulman et al in this supplement discusses hemorrhage associated with antithrombotic therapy.

*Clinical Risk Factors for Stroke in AF:* The risk of stroke among patients with AF not receiving anticoagulants has been studied in subjects participating in several randomized trials of antithrombotic therapy.<sup>11,20,41,113–115</sup> The most commonly cited risk schema are derived from the pooled analyses from the Atrial Fibrillation Investigators<sup>11</sup> and two analyses from the Stroke Prevention in Atrial Fibrillation (SPAF) investigators (Table 6).<sup>116,117</sup>

The Atrial Fibrillation Investigators group analyzed data from the pooled control groups of the first five primary prevention trials and found the following independent risk factors for stroke in AF: age (RR, 1.4 per decade); prior stroke or TIA (RR, 2.5); history of hypertension (RR, 1.6); and diabetes mellitus (RR, 1.7).<sup>11</sup>

The SPAF Investigators conducted a pooled anal-

ysis of 854 patients assigned to aspirin from the first two SPAF trials.<sup>117</sup> They identified three independent risk factors for stroke: the combination of female sex and age older than 75 years (RR, 3.7); systolic BP > 160 mm Hg (RR, 2.2); and impaired left ventricular function defined as a recent diagnosis of congestive heart failure or a fractional shortening < 25% by transthoracic echocardiography (RR 1.8). The SPAF Investigators extended their analysis of risk factors for stroke among the 2012 patients allocated to the aspirin or combination therapy arms of the SPAF I-III randomized trials as well as the SPAF III low-risk cohort treated with aspirin.<sup>116</sup> Five features were significantly associated with an increased risk of stroke: age (RR, 1.8 per decade); female sex (RR, 1.6); prior stroke or TIA (RR, 2.9); history of hypertension (RR, 2.0); and systolic BP > 160 mm Hg (RR, 2.3). Although diabetes was a univariate risk factor for stroke (RR 1.6), it was not a significant predictor in the multivariable model nor was impaired left ventricular systolic function or a history of coronary heart disease. Of note, when patients with a prior stroke or TIA were excluded from the analysis, female sex was no longer a significant predictor, but the other characteristics remained significant independent risk factors. This SPAF analysis provided an additional provocative finding that requires validation. Among women in the SPAF III studies without prior stroke or TIA, use of estrogen-containing hormone replacement therapy was found to be an independent correlate of stroke risk (RR, 3.2).

Studies from the large ATRIA AF cohort study largely confirmed the relative impact of the risk factors of prior stroke, hypertension, age, and diabetes.<sup>81</sup> These investigators also found that women with AF faced an increased risk of stroke (adjusted odds ratio, 1.6; 95% CI, 1.6 to 1.9) consistent with the Framingham Study analysis (described below).<sup>118,119</sup> The ATRIA results did not find this effect isolated to older women and also found no impact of estrogen replacement therapy on stroke risk.

Patients in the AFI analysis with coronary disease had an elevated crude annual risk of stroke (*eg*, 8.2% for those with a history of myocardial infarction).<sup>11</sup> However, in both the AFI and SPAF risk schemes, a history of coronary heart disease (*eg*, myocardial infarction or angina) was not an independent risk factor for stroke after adjusting for other stroke risk factors including prior stroke or TIA, age, diabetes, hypertension, and congestive heart failure/impaired left ventricular systolic function. Presumably, much of the elevated risk of stroke in patients with coronary heart disease is explained by coexisting vascular risk factors.

The independent contribution of severe hyperthy-

roidism, specifically thyrotoxicosis or thyroid storm, to the risk of stroke in AF is not well understood. AF develops in 10 to 15% of patients with thyrotoxicosis and is most common in patients  $\geq 60$  years of age, presumably reflecting an age-related reduction in the threshold for developing AF.<sup>120</sup> The prevalence of thyrotoxicosis in patients with AF is 2 to 5%.<sup>120</sup> Some studies<sup>121–125</sup> have reported a high frequency of stroke and systemic embolism in patients with thyrotoxic AF, although one study<sup>120</sup> did not find a statistically significant difference when patients with AF were compared to age- and sex-matched patients with NSR. Some of these studies have significant methodologic problems, which complicate interpretation of the results.<sup>120</sup> Accordingly, currently available studies have not confirmed that thyrotoxic AF is a more potent risk factor for stroke than other causes of AF. Since the incidence of thromboembolic events in patients with thyrotoxic AF appears similar to other etiologies of AF,<sup>120</sup> antithrombotic therapies should be chosen based on the presence of validated stroke risk factors (see Recommendations section).

*Comparison and Validation of Stroke Risk Stratification Schemes:* There are many published stroke risk stratification schemes for AF which have been proposed to identify “high risk” (who should be targeted for anticoagulation) and “low risk” patients with AF.<sup>126</sup> Most have been validated in trial populations. Earlier schemes tended to use two or three risk categories. Later, the CHADS<sub>2</sub> and Framingham risk scores provided a graded scale of risk with increasing numbers of risk factors.<sup>119,127</sup>

The AFI and SPAF-based risk stratification schemes are largely consistent with each other.<sup>11,116,117</sup> Prior stroke or TIA, older age, hypertension, and diabetes mellitus emerge from both analyses as risk factors for stroke in patients with AF. Unlike the AFI analysis, the later SPAF scheme found an adverse association with female sex and separated the effect of “hypertension” into an effect associated with the diagnosis itself and an effect due to elevated systolic BP at examination ( $> 160$  mm Hg). Another difference involves the observed absolute risks of stroke. For patients without a history of stroke or transient ischemic attack, the annual risk of stroke in the AFI data was 4.0% vs 2.7% in the SPAF data, although these estimates were based on relatively small numbers of thromboembolic events and 95% confidence bounds around the point estimates overlap. The apparent difference may be the result of variation in patient populations, chance, or a therapeutic benefit of aspirin among the SPAF participants. Such small differences can affect the decision to use anticoagulants in apparently lower risk patients. The differential impact of age in the

AFI and SPAF risk schema probably affects the greatest percentage of patients with AF. Specifically, the AFI scheme would consider all patients with AF aged 65 years or older at high risk for stroke, including those without any other risk factor for stroke. By contrast, the SPAF scheme would view women with AF  $\leq 75$  years of age and men of any age, without other risk factors, as at low risk of stroke. The resulting uncertainty about the risk faced by patients with AF age 65–75 years and men of any age without other risk factors applies to roughly 20% of the entire population with nonvalvular AF.<sup>111</sup>

On the basis of these analyses, the AFI and SPAF Investigators proposed stratifying patients with AF into different stroke risk categories. The AFI Investigators categorized patients with AF as at either high or low risk for stroke; high risk was defined as having any of the following characteristics: prior stroke or TIA, age  $\geq 65$  years, history of hypertension, or diabetes. Low risk was defined as the absence of these characteristics. Within the placebo arms of the analyzed trials, high risk patients suffered an increased annual risk of stroke (range 4.3%–8.1%) while low risk patients had a much lower annual risk of stroke of approximately 1.0%. The SPAF Investigators categorized subjects into three groups: high, moderate, and low risk of stroke (among patients taking aspirin). The features qualifying for these three risk strata are: (1) high risk (any of the following): prior stroke or TIA; women  $> 75$  years; age  $> 75$  years with a history of hypertension; or systolic BP  $> 160$  mm Hg (at any age); (2) moderate risk (any of the following): history of hypertension and age  $\leq 75$  years; or diabetes; and (3) low risk: no high or moderate risk features. Among patients without a prior stroke or TIA (*ie*, primary prevention), high-risk patients overall faced a 7.1% (5.4 to 9.5%) annual risk of stroke; moderate risk subjects had a 2.6% (1.9 to 3.6%) annual stroke risk; and low risk subjects had a 0.9% (0.6 to 1.6%) annual risk of stroke. Patients with multiple risk factors were at substantially higher stroke risk than those with one risk factor.<sup>115,116</sup>

A modified stroke risk classification scheme, CHADS<sub>2</sub>, integrates elements from the AFI and SPAF I–II schemes and was tested among 1733 hospitalized Medicare beneficiaries aged 65 to 95 years with nonvalvular AF that were not discharged on warfarin.<sup>127</sup> The CHADS<sub>2</sub> risk index uses a point system in which two points are given for a history of stroke or TIA, and one point each for age  $\geq 75$  years, a history of hypertension, diabetes, or recent congestive heart failure. The rate of stroke increased with an increasing CHADS<sub>2</sub> score in this elderly cohort, although few patients had a very high score of  $\geq 5$ , and  $< 7\%$  had a score of zero (Table 7). Modified

**Table 6—Comparison of Clinical Risk Factors for Stroke in AF in Randomized Trials of Antithrombotic Therapy (Section 1.1.13)\***

Characteristics	Atrial Fibrillation Investigators <sup>11</sup>		SPAF I–II† <sup>117</sup>		SPAF I–III‡ <sup>116</sup>	
	RR	Annual Risk	RR (95% CI)	Annual Risk	RR	Annual Risk
Age, per decade	1.4	NA	3.7 (2.2–6.2)§	10.4%	1.8	NA
Female	NS	NA			1.6	NA
Prior stroke or TIA	2.5	11.7%	NS	6.4%	2.9	13.0%
Hypertension	1.6	5.6%	2.2 (1.3–3.6)	7.6%	95% CI 2.0–2.3¶	NA
Diabetes mellitus	1.7	8.6%	NS	NA	NS	NA
Congestive heart failure	NS	6.8%	1.8 (1.1–3.0)#	5.5%	NS	NA
Coronary heart disease	NS	95% CI 6.7–8.2	NS	NA	NS	NA

\*NS = not statistically significant. See Table 2 for expansion of abbreviation.

†Among pooled aspirin arms of two trials.

‡Among pooled aspirin arms of SPAF I and II trials, SPAF III aspirin cohort, and SPAF III aspirin plus low-dose warfarin (target INR > 1.5).

§RR refers to the combination of being female and ≥ 75 yr old.

||Defined as systolic BP > 160 mm Hg.

¶History of hypertension (RR 2.0), systolic BP > 160 mm Hg (RR 2.3).

#Defined as diagnosed congestive heart failure within 100 days or a fractional shortening ≤ 25% by echocardiography.

AFI and SPAF I–II risk schemes were also tested in this cohort. The modified AFI scheme had high (prior stroke or TIA, hypertension, or diabetes) and moderate (age > 65 years and no high-risk features) risk categories, corresponding to stroke rates (per 100 person-years) of 5.4 (4.2 to 6.5) for high risk and 2.2 (1.1 to 3.5) for moderate risk persons. The modified SPAF I–II scheme had high (prior stroke or TIA, women > 75 years, or recent congestive heart failure diagnosis), moderate (hypertension diagnosis and no high risk features), and low risk (no moderate or high risk features) categories. In this cohort, SPAF I–II high-risk persons had a stroke rate of 5.7 (4.4 to 7.0), moderate risk persons had a rate of 3.3 (1.7 to 5.2), while low-risk subjects had a rate of 1.5 (0.5 to 2.8).

A study from the Framingham Heart Study examined risk factors for stroke among 705 patients with new-onset AF, after excluding patients who suffered an ischemic stroke, TIA, or death within 30 days of the AF diagnosis.<sup>119</sup> The only significant multivariable predictors of ischemic stroke off oral VKAs were age per decade (RR, 1.3), female sex (RR, 1.9), prior stroke or TIA (RR, 1.9), and diabetes (RR, 1.8), which are consistent with prior studies as described above, with the exception that systolic BP was not found to be an independent predictor of stroke in this population. Using a scoring system that assigned points according to age, sex, systolic BP, and the presence of diabetes, prior stroke or TIA, the proportion of newly diagnosed AF patients considered at “low-risk” varied from 14.3 to 30.6% if the threshold annual predicted rate of stroke ranged from ≤ 1.5 per 100 person-years to ≤ 2 per 100 person-years (actual observed annual stroke rates of 1.1 to

1.5, based on total of 88 validated strokes). As expected, there was variation in the proportion of patients considered “low-risk” by the AFI (6.4%), SPAF (17.3%), and CHADS<sub>2</sub> (10.2%) risk schemes. The observed annual stroke rates in these differently defined low-risk categories of patients were: AFI: 0.9%; SPAF: 2.3%; and CHADS<sub>2</sub>: 1.7%.

The AFI, SPAF, and Sixth ACCP Consensus Conference (ACCP-6)<sup>128</sup> risk schemes were assessed in the Cardiovascular Health Study. Among 259 elderly (≥ 65 years) participants with nonvalvular AF in this research cohort, annual rates of stroke using modified AFI/ACCP-6 criteria were 2.7% (1.7 to 4.1%) for high risk (prior stroke or TIA, hypertension, diabetes, congestive heart failure, or coronary heart disease) and 2.4% (0.9 to 5.1%) for moderate risk (age ≥ 65 years and no high risk features) subjects off anticoagulation.<sup>129</sup> Using the SPAF III criteria, annual stroke rates were relatively similar, ranging from 3.7% (2.1 to 5.8%) for high risk (prior stroke or TIA, women > 75 years old, systolic BP > 160 mm Hg, or impaired left ventricular systolic function), 2.0% (0.7 to 4.7%) for moderate risk (history of hypertension and no high risk features), and 1.7% (0.6 to 3.8%) for low risk (no moderate or high risk features). Among 1073 patients without prior stroke or TIA who participated in the SPAF III trial’s aspirin plus low-dose warfarin arm or SPAF III aspirin cohort study, the AFI, ACCP, and SPAF I–II criteria were evaluated.<sup>130</sup> The stroke rates for each risk stratum differed across the different risk schemes, with consistently low stroke rates in the low risk categories for all schemes but significant variation in the moderate to high risk categories as well as the proportion of subjects in each category.

The AFI, SPAF, ACCP 6, CHADS<sub>2</sub>, and Framingham risk schema were compared using the pooled individual data from aspirin treated arms from five randomized trials.<sup>131</sup> These included primary and secondary prevention trials with an overall annualized rate of stroke in the aspirin arms of 4.2%. All schema could be adapted to identify a low-risk group (annualized rate of 0.9 to 1.4%) and a “high-risk” group (annualized rate of 3.0 to 5.3%) and an intermediate-risk group (annualized rate of 1.0 to 3.2%), though this last category tended to overlap substantially with adjacent categories. The various risk schema assigned very different proportions of patients into the three categories of risk. For example, 49% of patients were considered low-risk using the Framingham scheme as compared to 8.7% of patients using the ACCP-6 scheme. However, these proportions reflected different risk thresholds (eg, 1.4%/yr vs 0.5%/yr for Framingham and ACCP-6, respectively). Using the c-statistic criterion for discrimination, CHADS<sub>2</sub> was marginally better than the other schema, with a c-statistic of 0.70, likely reflecting its higher weighting of the impact of prior stroke. When these schema were assessed among patients who had not had a prior stroke, CHADS<sub>2</sub> was still marginally better than the other schema, but with a diminished c-statistic of 0.63. Since prior stroke is universally recognized as a strong indication for VKA therapy, performance of risk schema among primary prevention patients is the pressing clinical need. C-statistics in the 0.58 to 0.63 range are mediocre.<sup>132</sup>

*Risk Stratification Schemes in Other Guidelines:* The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology management guidelines for AF classify those at ‘high risk’ as those with prior thromboembolism (stroke, TIA, systemic embolism), rheumatic mitral stenosis, or more than one of: age ≥ 75 years, hypertension, heart failure, impaired LV systolic function, or diabetes mellitus.<sup>108</sup> “Moderate risk” is where there is only one of: age ≥ 75 years, hypertension, heart failure, impaired LV systolic function, or diabetes mellitus. “Low risk” are essentially those with AF with no risk factors. Less validated or weaker risk factors in this schema were female gender, age 65 to 74 years, coronary artery disease or thyrotoxicosis. Broadly, the high risk category refers to CHADS<sub>2</sub> scores of ≥ 2, where warfarin is recommended; the intermediate risk corresponds to a CHADS<sub>2</sub> score of 1, where warfarin or aspirin 81 to 325 mg/d is recommended; and the low risk category refers to a CHADS<sub>2</sub> score of 0, where aspirin 81 to 325 mg is recommended. The 2006 American College of Cardiology/American Heart Association/European Soci-

ety of Cardiology schema has not been prospectively validated.

In 2006, the UK National Institute for Health and Clinical Excellence (NICE) published the UK national guidelines for AF management, which proposed an algorithm-based stroke risk stratification which is largely based on the AFI-scheme.<sup>133</sup> The NICE risk stratification schema has been compared against the CHADS<sub>2</sub> in a prospective cohort, and the accuracy of both clinical risk stratification schemes were found to be similar for predicting stroke and vascular event rates.<sup>134</sup>

*Echocardiographic Predictors of Stroke in AF:* An AFI analysis of transthoracic echocardiograms done in three of the original trials found that moderate-to-severe left ventricular systolic dysfunction was an incremental, strong risk factor above clinical risk factors (RR, 2.5), but left atrial diameter was not independently related to risk of stroke in AF after adjusting for other clinical risk factors.<sup>113</sup> While left atrial size and left ventricular systolic function can be adequately assessed by transthoracic echocardiography, transesophageal echocardiography (TEE) is needed to consistently visualize important abnormalities of the left atrium and aortic arch. This modestly invasive approach is commonly used as an adjunct to elective cardioversion (see below), but it has also been applied to studies of outpatients with chronic AF.<sup>135,136</sup> Visible thrombus and dense spontaneous echo contrast (a marker of blood stasis) in the left atrium conferred a twofold to fourfold increase in risk of subsequent stroke. More than 90% of these thrombi involve or are confined to the left atrial appendage.<sup>16,137</sup> In addition, patients with TEE-detected aortic plaques with complex features (mobile, pedunculated, ulcerated, or > 4 mm in thickness) had extremely high stroke rates in the SPAF III study. Of note, many of these abnormalities were

**Table 7—Risk of Stroke (Section 1.1.13)\***

CHADS <sub>2</sub> Score	Patients (n = 1,733), No.	Adjusted Stroke Rate per 100 Person-yr† (95% CI)
0	120	1.9 (1.2–3.0)
1	463	2.8 (2.0–3.8)
2	523	4.0 (3.1–5.1)
3	337	5.9 (4.6–7.3)
4	220	8.5 (6.3–11.1)
5	65	12.5 (8.2–17.5)
6	5	18.2 (10.5–27.4)

\*According to CHADS<sub>2</sub> score.<sup>127</sup>

†The adjusted stroke rate was the expected stroke rate per 100 person-years derived from the multivariable model assuming that aspirin was not taken.

observed in the descending aorta.<sup>136</sup> Additional TEE measures have been suspected as risk factors for stroke (eg, depressed left atrial appendage flow velocity; ie, <20 cm/s). At present, however, there is no clear evidence that TEE findings add sufficient independent information to stroke risk stratification for most patients with chronic AF, when clinical and transthoracic echocardiographic risk factors are considered, to merit the additional risks, discomfort, and costs.

*Other Potential Risk Factors for Stroke in AF:* Other potential risk factors that may refine current clinical and echocardiographic stroke risk schemes include genetic polymorphisms, abnormalities in hemostatic and thrombotic factors, platelet activation and aggregation pathways, and endothelial or vascular dysfunction.<sup>129,138,139</sup> The pathophysiology of thromboembolism in AF is multifactorial, but it appears that AF confers a prothrombotic or hypercoagulable state.<sup>140</sup> Indeed, patients with AF demonstrate abnormalities of hemostasis, platelets and endothelial function, which have been shown to be independent of associated structural heart disease or underlying etiology of AF. This prothrombotic state can be altered by cardioversion and antithrombotic therapy. Recent studies have suggested that elevated levels of plasma biomarkers, such as von Willebrand factor (an index of endothelial damage/dysfunction), fibrin d-dimer (an index of fibrin turnover and thrombogenesis) and interleukin-6 (an index of inflammation) may be predictive of subsequent cardiovascular events in patients with AF, independent of known clinical risk factors.<sup>141</sup> In particular, plasma von Willebrand factor (a marker of endothelial damage/dysfunction) levels may add information to clinical risk stratification schemes.<sup>134</sup> However, at this point, there is not sufficient supportive evidence to include such biomarkers as standard risk factors for stroke in AF.

*Pattern of AF and Risk of Stroke:* A recurrent clinical concern is whether patients with paroxysmal, or intermittent, AF (PAF) face the same risk of stroke as those with persistent, ie, sustained AF. Periods of NSR should theoretically lessen the risk of stroke, yet transitions from AF to NSR may acutely heighten risk in a manner similar to the increase in risk caused by cardioversion (see below). Retrospective studies suggested that PAF is associated with a lower risk of stroke than chronic AF.<sup>120,142</sup> However, when associated stroke risk factors are controlled for, clinical trial data suggest that PAF confers a relative risk of stroke similar to persistent or permanent AF.<sup>11,143</sup> Patients with PAF are generally younger and have a lower prevalence of associated clinical

risk factors than those with persistent AF; therefore, their absolute stroke rate is lower. The relative risk reduction provided by warfarin also appears similar for patients with paroxysmal AF and persistent AF. This conclusion, however, is limited by the relatively small number of patients with PAF participating in the trials (about 12% of subjects in the first 5 randomized trials).<sup>11</sup> Analyses of PAF are further complicated by the fact that patients with PAF differ greatly in the frequency and duration of AF episodes<sup>144</sup> and differences across studies in the definition of PAF. Studies of PAF are also limited by significant differences in patient awareness of episodes of AF. Indeed, studies document a high prevalence of asymptomatic PAF, even among patients who are symptomatic with some episodes.<sup>145–147</sup> There is some evidence suggesting that stroke risk in patients with PAF increases with more time spent in AF.<sup>148,149</sup> This relationship is being explored using implanted devices that can report episodes of AF in patients with PAF.<sup>150</sup> Despite the uncertainty in the underlying evidence, it seems reasonable to treat patients with PAF in a manner similar to those with persistent AF, basing use of anticoagulants on the presence of risk factors for stroke.

*Are Absolute Rates of Stroke With AF Lower Today Than During the Period of the Original Trials of VKA Therapy?:* Most stroke risk stratification schemes for patients with AF are based on the placebo or aspirin arms of the early trials of VKA treatment conducted in the 1980s and early 1990s. There is accumulating evidence that the absolute risk of stroke faced by patients with AF is lower currently than when the initial trials were conducted. This appears to translate into lower risks across risk strata. In the metaanalysis of the first five primary prevention trials of VKA therapy the overall annual rate of stroke in the placebo arms was 4.5%.<sup>11</sup> This contrasts with an annual rate of 2.4% in the more recently assembled ATRIA cohort.<sup>81</sup> In the SPAF III trial that enrolled patients with at least one risk factor the overall annual rate of thromboembolism was 7.9% in the aspirin plus mini-warfarin arm.<sup>28</sup> This contrasts with a rate of 2.2%/year in the clopidogrel plus aspirin arm of the ACTIVE-W trial conducted a decade later which selected patients in a manner similar to the SPAF III trial.<sup>32</sup> In both SPAF III and ACTIVE-W, VKA therapy was far superior to the comparator and the difference in the rates in the trials' respective antiplatelet therapy arms is not explainable by putative effect of clopidogrel. Focusing specifically on patients in the intermediate risk stratum of CHADS<sub>2</sub> = 1, a prior metaanalysis estimated a stroke risk of 2.2%/year.<sup>131</sup> In the ATRIA

study the risk faced by patients in the CHADS<sub>2</sub> = 1 stratum was 1.5%/year.<sup>81</sup>

Recent trials comparing novel antithrombotic therapies vs warfarin do not provide a placebo or aspirin arm. However, the experience of the warfarin arms of these trials also supports lower stroke risk among patients with AF in the current era. In the SPORTIF V trial, which recruited higher risk patients, 74% of patients had two or more risk factors. Yet, the rate of stroke was only 1.1%/year.<sup>31</sup> Similarly, in the ACTIVE-W trial, the rate of stroke among patients assigned to warfarin was 1.0%/yr.<sup>32</sup> By contrast, the rate of stroke in the adjusted-dose warfarin arm of SPAF III was 1.9%/yr.<sup>28</sup> Overall, it appears that stroke risk faced by patients with AF is lower currently, perhaps because of more effective reduction of modifiable risk factors.<sup>151,152</sup> This lower estimated stroke risk will affect the risk factor-based thresholds for VKA therapy that we present below.

*Optimal Intensity of Anticoagulation for AF:* There are only limited data directly comparing different intensities of OAC in patients with AF.<sup>28</sup> However, the results of the randomized trials and observational studies of clinical practice provide fairly consistent evidence about the optimal level of anticoagulation for AF. The initial set of randomized trials of OAC vs control employed a range of target intensities, both PTR based and INR based. The BAATAF<sup>23</sup> and SPINAF<sup>24</sup> studies used the lowest target intensity, PTR 1.2 to 1.5, corresponding roughly to an INR range of 1.4–2.8. Anticoagulation appeared just as effective at preventing strokes in these trials as in the others using higher target intensities. A target INR of 1.2 to 1.5 was ineffective in the high-risk SPAF III trial, even when combined with aspirin at 325 mg/d.<sup>28</sup> No randomized trials have compared target intensities between an INR of 1.5 to 2.0 (without an additional antiplatelet agent) with an INR between 2.0 and 3.0. One trial compared an INR range of 1.1 to 1.6 with a range of 2.5 to 3.5.<sup>55</sup> No difference in efficacy was detected; however, the low event rates in this study limited the power to detect a difference. The EAFT study found a decrease in efficacy below an INR of 2.0,<sup>21</sup> but the trial could not assess finer gradations in INR below 2.0.

The data needed to precisely describe stroke risk as a function of INR are formidable. The problem is similar to, but less extreme, than that for describing risk of ICH as a function of INR. In the trials of adjusted dose VKA therapy in AF relatively few thromboembolic events on anticoagulants have been observed. This was particularly the case in the trials of adjusted dose VKA therapy vs control or aspirin-containing regimens where many of the trials were

stopped early because of the evident efficacy of adjusted dose anticoagulation. In such circumstances, observational studies can be particularly informative because they can accumulate much larger numbers of outcome events. A case-control study based in a large anticoagulation unit found that the risk of stroke increased at INR levels < 2.0.<sup>153</sup> The odds of stroke doubled at an INR of 1.7 and tripled at an INR of 1.5 compared to an INR of 2.0, and increased even more dramatically if the INR was < 1.5. A second hospital-based case-control study also found a sharp increase in risk of stroke among patients with AF and INR values lower than 2.0. INR levels > 2.0 do not appear to further lower the risk of ischemic stroke.<sup>153,154</sup> Longitudinal analyses from the ATRIA cohort study support these findings with a nearly fivefold increase in rate of ischemic stroke at INR levels of 1.5 to 1.9 compared to 2.0 to 2.5.<sup>58</sup> *Post-hoc* analyses of the SPAF III trial were also consistent with these epidemiologic analyses.<sup>28</sup> It is worth noting that such analyses from randomized trials do not benefit from randomization since patients are not randomly assigned to different INR levels. Such studies are effectively observational cohort studies of the impact of INR levels using data from randomized trials.

The optimal level of anticoagulation in AF is one that preserves efficacy in preventing ischemic strokes while minimally increasing the risk of major hemorrhage, especially ICH. Risk of ICH is fairly low at INR values < 4.0 but increases sharply at higher INR levels.<sup>39,155,156</sup> As noted above, the risk of ischemic stroke is low at INR values down to 2.0. INR levels below 2.0 not only increase the risk of stroke but also markedly raise the risk of severe or fatal stroke should such an event occur.<sup>58,157</sup> Since randomized trials have successfully used INR targets of 2.0 to 3.0, this target range seems an appropriate standard. There is currently no direct evidence indicating that this range should be changed for older patients (> 75 years), who have higher risks than younger patients of both stroke off anticoagulants and bleeding on anticoagulants.<sup>36,39,52,156,158–160</sup> One recent set of guidelines suggested using a target INR of 1.6–2.5 for older patients at increased risk of bleeding and for other patients at higher risk of stroke who couldn't tolerate full dose anticoagulation.<sup>108</sup> However, observational data indicate that INRs of < 2.0 are not protective against ICH when compared to an INR range of 2.0 to 3.0, even in older patients.<sup>39</sup> Lower target INR ranges would expose many patients to periods of relatively ineffective anticoagulation without significant reduction in the risk of ICH. Tight control near an INR level of 2.5 seems a preferable strategy based on existing evidence.

The NASPEAF trial suggests that one may be able to target modestly lower INR levels and still maintain very high efficacy if anticoagulation is combined with an antiplatelet agent.<sup>17</sup> These provocative results should be confirmed before clinical recommendations can be made regarding such a strategy.

#### 1.1.14 Patient Preferences and Decision Analyses

Anticoagulation poses a significant hemorrhagic risk. Oral VKAs also impose other lifestyle constraints on patients such as dietary modifications and frequent monitoring of anticoagulation intensity. As a result, patient education and involvement in the anticoagulation decision is important. Many patients with AF have a great fear of ischemic stroke and choose warfarin even for a relatively small decrease in the absolute risk of stroke,<sup>161,162</sup> while others at relatively low risk for stroke want to avoid the burdens and risks of VKAs and opt for aspirin.<sup>161,163,164</sup> The safe use of anticoagulants depends on patient cooperation and a monitoring system that can achieve INR targets on a regular basis. Findings of the randomized trials suggest that anticoagulation at an INR of 2.0 to 3.0 can be adequately safe even for elderly patients, and the ISCOAT and ATRIA experiences demonstrate that low hemorrhage rates can be achieved in clinical practice outside of trials, particularly if well-organized anticoagulation clinics are involved.<sup>11,52,54,81,159</sup>

In addition to clinical risk stratification, patient perspectives and preferences should be incorporated into the decision about antithrombotic therapy. Prior studies have shown that patient and physician perspectives often differ, with patients generally placing more value on the prevention of stroke than avoiding a major hemorrhage as compared with physicians.<sup>162</sup> Many patients, in fact, assign utilities to a moderate to severe stroke that are equivalent or worse than death.<sup>164,165</sup> Ethnic and cultural differences in patient perceptions of AF and antithrombotic therapy exist.<sup>166</sup> Such differences can affect worldwide use of anticoagulant therapy in AF patients.

Decision analysis techniques have been used to evaluate the projected net benefit or harm associated with different antithrombotic treatment strategies in AF.<sup>163,167,168</sup> These models formally combine the absolute risks associated with patient characteristics, estimates of the efficacy and safety of antithrombotic treatment, and assigned values (utilities) of related health states (*eg*, taking warfarin, suffering a major stroke) trials. Sensitivity analyses test the impact of varying assumptions made in the model. In general, published decision analyses support the net benefit of anticoagulation with oral VKAs for patients with

AF at moderate to high risk for stroke but not very high risk of bleeding. However, the treatment threshold for these levels of risk and the criteria for moderate and high risk categories vary across studies, reflecting the need for more refined estimates.<sup>167</sup> The decision analysis approach has been modified in attempts to help individual patients make better choices about antithrombotic therapy in AF.<sup>163</sup> Strong evidence is currently lacking, however, that these decision support tools improve clinical outcomes.<sup>169</sup>

*Use of Antithrombotic Therapy for AF in Clinical Practice:* Multiple studies of practice patterns of use of VKAs for AF have been reported.<sup>8,95,102,170–177</sup> The following broad generalizations appear to hold: (1) in North America and Western Europe the use of VKAs for AF has increased greatly from the early 1990s to the present. Currently, 50% or more of AF patients are treated with VKAs; (2) use of VKAs is moderately higher in patients at increased risk for ischemic stroke and moderately lower in patients at increased risk of bleeding; however, the use of VKAs decreases with age > 80 years despite the fact that such patients are at higher risk of ischemic stroke; many patients at apparently low risk for stroke are treated with VKAs and many patients at higher risk for stroke, *eg*, those status post an ischemic stroke, are not treated with VKAs; and (3) detailed clinical assessment of high-risk patients not receiving VKA therapy reveals that many of such patients have clear physical or cognitive contraindications for anticoagulants.<sup>175,178</sup> In contrast to the generally aggressive use of anticoagulants for AF in North America and Western Europe, physicians in Japan are reluctant to prescribe VKAs for AF, presumably reflecting a greater fear of hemorrhagic stroke. When VKAs are prescribed in Japan, lower INR levels are targeted.<sup>179–181</sup>

#### 1.1.15 Managing Anticoagulant Therapy for AF

General recommendations regarding management of OAC are given in the chapters by Ansell et al in this supplement. The urgency of anticoagulation for patients with AF depends on the risk factor status of individual patients. In general, the short-term (*ie*, up to two weeks) risk of stroke in patients with AF is quite low since the annual risk even among the highest risk individuals is < 15%. As a result, stable patients with AF can be anticoagulated on an outpatient basis with VKAs, such as warfarin, alone. For particularly worrisome patients, physicians may be more comfortable with a heparin/warfarin bridging regimen. This same general approach applies to interruptions of anticoagulation necessitated by sur-

gery or related procedures (see the relevant chapter by Ansell et al in this supplement). For most patients with AF, warfarin can be stopped several days before the procedure and restarted shortly after the procedure without any need for heparin in the interim. Again, for patients at particularly high risk of thromboembolism or for patients at higher risk in whom the interruption will exceed two weeks, a heparin/warfarin bridging regimen should be considered.

Anticoagulation should be managed in a highly organized manner, preferably through specialized anticoagulation clinics. The relevant chapter by Ansell et al in this supplement covers these crucial aspects of maximizing the quality of anticoagulation management. For a discussion of when to begin anticoagulation after a stroke in patients with AF, please refer to the chapter by Albers et al in this supplement.

#### 1.1.16 Summary: State of the Science

It is remarkable that 15 years after the publication of multiple definitive trials demonstrating the extraordinary efficacy of anticoagulants in preventing stroke in AF and after several more recent very large and rigorous trials have validated the efficacy and safety of anticoagulants in AF, there remains considerable controversy about which patients with AF should be treated with long-term VKA therapy. Indeed, some recent revised guidelines have been even more restrictive in recommending anticoagulant therapy for patients with AF.<sup>108,182</sup> To help explain this apparent paradox we will briefly review the elements of the anticoagulation decision and the evidence underlying each component. More detailed discussion can be found above.

**1. The Efficacy of VKA Therapy:** Trials of adjusted-dose VKA therapy reveal a relative risk reduction for ischemic stroke of two thirds by intention-to-treat analysis. This relative efficacy is extraordinary by itself, but even more impressive given the fact that most individuals assigned to VKA therapy who sustained an ischemic stroke in the trials had either stopped taking anticoagulants or were clearly underanticoagulated at the time the stroke occurred. These quantitative results indicate that adjusted-dose VKA therapy essentially reverses the stroke risk posed by AF. VKA therapy prevents severe/fatal ischemic stroke as well as less disabling strokes. It is generally assumed that the relative risk reduction of VKA therapy applies to all AF patient risk groups. This seems a reasonable generalization from the trial data but other patterns could apply, *eg*, if there were a different proportion of cardioembolic strokes in any patient subgroup.

**2. The Safety of VKA Therapy in AF:** The risk of major hemorrhage due to adjusted-dose VKA therapy was small in most trials. Importantly, the incremental risk of ICH due to VKA therapy, the cause of most fatal or disabling bleeding events,<sup>26</sup> was generally  $< 0.3\%/yr$ . Observational studies, which can accumulate many more events than trials, make clear that risk of ICH is highest among the oldest patients with AF and among those who have sustained a prior stroke. Of course, these individuals are also at high risk of ischemic stroke without VKA therapy.

**3. The Optimal INR Target:** The INR target of 2.0–3.0 was extremely effective in the SPAF III study,<sup>28</sup> and has continued to demonstrate efficacy and safety in recent large trials vs novel antithrombotic treatments.<sup>32,80</sup> Two of the original successful trials, done in America, likely used slightly lower anticoagulation intensities,<sup>23,24</sup> but this assertion is uncertain since these trials used PTR rather than INR targets and used a variety of thromboplastins, making translation of PTRs to INRs problematic. Observational studies provide more precise information about efficacy and safety across the range of INR levels. These studies make clear that risks of both ischemic stroke and of ICH are extremely sensitive to the INR level. The risk of ischemic stroke rises very rapidly as INR levels fall below 2.0. Two-thirds of ischemic strokes occurring among patients taking VKAs occur at INR levels below 2.0. There is no increase in efficacy at INR levels  $> 3.0$ .<sup>28,58,153</sup> Indeed, there is no clear increase in efficacy at INR levels  $> 2.0$ . Risk of ICH is a similar but mirror-imaged function of INR levels, with a sharp increase in risk seen at INRs of 3.5 to 4.0 and above. Importantly, there is no decrease in risk of ICH on VKAs at INR levels  $< 2.0$ .<sup>39</sup> Targeting INR levels  $< 2.0$  increases risk of ischemic stroke without decreasing risk of ICH. These powerful observational INR analyses strongly support the target INR of 2.0 to 3.0, which has been used successfully in multiple recent trials. If INR control were more precise, then a narrower INR target  $> 2.0$  might be more appropriate. But, even in the controlled environment of trials, only two-thirds of INR values fall in the 2.0 to 3.0 range. Lower INR target levels will result in patients spending more time at unprotective INR levels. Narrower INR targets may be unrealistic and may produce unintended swings in INR control.

**4. The Efficacy of Aspirin:** As we discuss above, aspirin provides little protection against stroke in AF. There was a small signal in the original set of trials in favor of aspirin vs placebo, but these results were

also highly consistent with no effect. Importantly, there was never any evidence that aspirin protected against severe/fatal ischemic stroke that occurs more commonly with AF. The subsequent SPAF III and BAFTA trials and the very large ACTIVE-W trial emphatically demonstrated that adjusted-dose VKA therapy was far superior to aspirin-containing regimens. While massive meta-analyses demonstrate an efficacy of aspirin of about 25% in other cardiovascular conditions, such analyses are of questionable relevance to AF.<sup>183</sup> Guidelines typically pose aspirin as the less effective but safer alternative therapy for stroke prevention in AF. Such a comparison can be misleading since it does not convey the reasonable concern that aspirin's efficacy is quite small.

5. *Translation Into Usual Care:* High-quality randomized trials should generate internally valid results about the efficacy of a therapy. Design features of such trials may raise concern about the generalizability of trial results in usual clinical care. Regarding VKA therapy for AF, such features include selection of patients at lower risk for bleeding or nonadherence with INR testing or dose changes, explicit or effective exclusion of very old and/or very complex and/or frail patients, and very high quality management of INR testing and dose adjustments. In addition, the average patient follow-up in trials of VKA therapy for AF has been about 1.5 years, yet anticoagulants are indicated for lifelong treatment. Recent studies generally support the translation of the efficacy and safety of VKAs into usual clinical care, with the proviso that some studies have reported reduced relative risk reductions for stroke compared to the trials. Such reduction in RRR may have resulted, at least in part, from errors in event adjudication or anticoagulation status as a consequence of using administrative databases. INR control in clinical care can approach that of the RCTs but there may be more gaps in INR testing than in RCTs.<sup>32,81</sup> There is evidence that patients initiating VKA treatment suffer higher rates of bleeding and that trials, especially recent trials, have predominantly recruited prevalent as opposed to new users. Concern that bleeding risks, particularly risk of ICH, are higher in usual clinical care than seen in RCTs, is a major reason for raising the threshold for use of anticoagulants in AF.

6. *Predicting Risk, Particularly Absolute Risk of Stroke Among Untreated Patients With AF:* VKA therapy has been successful in randomized trials that have enrolled AF patients across the spectrum of stroke risk. Nonetheless, all guidelines have adopted a strategy of recommending anticoagulants for patients at higher untreated risk of ischemic stroke. It

is assumed in these recommendations that the approximately 67% RRR<sup>11</sup> will generalize to all patient subgroups. Recommended restrictions in use of anticoagulants reflect concern that patients at low untreated risk of ischemic stroke will gain little absolute reduction in stroke risk while incurring sizable risk of hemorrhage and burden of VKA management. However, there are major uncertainties affecting this approach. Predicting absolute stroke risk is uncertain. Risk stratification schemes are mediocre, particularly among the many AF patients who have not had a prior stroke.<sup>131</sup> Further, these risk schema predict relative risk or rank order, but not necessarily absolute risk. There also may be important secular changes in stroke risk.<sup>10</sup> Absolute risks of stroke faced by AF patients today appear to be lower than the risks faced in the early trials, perhaps because of better control of BP<sup>151,152</sup> and cholesterol levels, and perhaps because of lower BP thresholds for diagnosing hypertension.<sup>151</sup> Finally, absolute reduction in risk of ischemic stroke is only half of the risk calculation. The other half, absolute increase in risk of hemorrhage—particularly ICH—is not well estimated at the level of patient subgroups. All these uncertainties are aggravated by the fact that we are dealing with low annual rates of potentially devastating events. While there is likely consensus that most AF patients facing a risk of at least 4%/yr should take anticoagulants and most AF patients facing a risk of < 1%/yr should not take anticoagulants, there is uncertainty about use of anticoagulants between these risk levels and considerable uncertainty in specifying just where an individual AF patient's risk falls. Different decisions about the risk threshold for use of anticoagulants can potentially affect large fractions of all patients with AF.

In sum then, we know with great confidence that VKA therapy targeted at INR 2.0 to 3.0 will prevent AF-related ischemic stroke in the vast majority of patients with AF. We know, as well, that patients at low untreated risk of stroke have less to gain from VKA therapy. We are less secure in specifying an individual AF patient's absolute risk of ischemic stroke and probably even less informed about their absolute risks of ICH. Recent studies of AF suggest that risks of ischemic stroke are lower today than in the past. But trials and recent observational studies also are generally reassuring about the safety of VKA therapy. In the following, we recommend use of anticoagulant therapy based on risk factors for ischemic stroke in AF. Because of the exemplary performance of VKAs in randomized trials across the spectrum of stroke risk, we tend to favor use of VKAs down to intermediate levels of stroke risk. We view aspirin therapy as a minimally effective alternative to VKAs. Finally, we believe in engaging the patient in

the anticoagulation decision. However, we anticipate that many patients will ultimately defer to their physician because the decision is so complex, involving a balance of small but real risks of potentially devastating outcomes, and uncertainties about an individual patient's set of risks. We emphasize that the anticoagulation decision is not a one-time action but needs to be revisited in light of a patient's experience, preferences, and changing risk status.

## Recommendations

**1.1.1. In patients with AF, including those with paroxysmal AF, who have had a prior ischemic stroke, transient ischemic attack, or systemic embolism, we recommend long-term anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) because of the high risk of future ischemic stroke faced by this set of patients (Grade 1A). Timing of the initiation of VKA therapy after an acute ischemic stroke involves balancing the risk of hemorrhagic conversion with short-term risk of recurrent ischemic stroke and is addressed in the chapter by Albers et al in this supplement.**

**1.1.2. In patients with AF, including those with paroxysmal AF, who have two or more of the following risk factors for future ischemic stroke, we recommend long-term anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) because of the increased risk of future ischemic stroke faced by this set of patients (Grade 1A).**

**Two or more of the following risk factors apply: age > 75 years, history of hypertension, diabetes mellitus, and moderately or severely impaired left ventricular systolic function and/or heart failure.**

Remark: Recommendations 1.1.1 and 1.1.2 correspond to a recommendation of oral VKA therapy for individuals with a score  $\geq 2$  using the CHADS<sub>2</sub> classification. For these and all other Recommendations of long-term therapy in this chapter, *long-term* means lifelong unless a contraindication emerges.

**1.1.3. In patients with AF, including those with paroxysmal AF, with only one of the risk factors listed below, we recommend long-term antithrombotic therapy (Grade 1A), either as anticoagulation with an oral VKA, such as warfarin, targeted at an INR of 2.5 (range, 2.0 to 3.0) (Grade 1A), or as aspirin, at a dose of 75 to 325 mg/d (Grade 1B). For these patients at intermediate risk of ischemic stroke, we suggest a VKA rather than aspirin (Grade 2A). This set of patients with AF is defined by having one of the**

**following risk factors: age > 75 years, history of hypertension, diabetes mellitus, and moderately or severely impaired left ventricular systolic function and/or heart failure.**

**1.1.4. In patients with AF, including those with paroxysmal AF, aged  $\leq 75$  years and with none of the other risk factors listed above, we recommend long-term aspirin therapy at a dose of 75 to 325 mg/d (Grade 1B) because of their low risk of ischemic stroke.**

*Underlying values and preferences:* Anticoagulation with oral VKAs, such as warfarin, has far greater efficacy than aspirin in preventing stroke, and particularly in preventing severe ischemic stroke, in AF. We recommend the option of aspirin therapy for lower risk groups in 1.1.3 and 1.1.4, above, estimating the absolute expected benefit of anticoagulant therapy may not be worth the increased hemorrhagic risk and burden of anticoagulation. Individual lower-risk patients may rationally choose anticoagulation over aspirin therapy to gain greater protection against ischemic stroke if they value protection against stroke much more highly than reducing risk of hemorrhage and the burden of managing anticoagulation. Our recommendations assume that the patient is not at high risk for bleeding and that good control of anticoagulation will occur.

Remarks: 1. These recommendations apply to patients with persistent or paroxysmal AF and not to patients with a single brief episode of AF due to a reversible cause, such as an acute pulmonary infection. 2. The optimal dose of aspirin for patients with AF is unclear. The largest effect of aspirin was seen in the first Stroke Prevention in AF (SPAF I) trial, which used aspirin at 325 mg/d.<sup>1</sup> However, generalizing from trials of aspirin for all antithrombotic indications and from physiologic studies, we feel the best balance of efficacy and safety is achieved at low doses of aspirin, *ie*, 75 to 100 mg/d (see the chapter by Patrono et al in this supplement).<sup>2</sup>

## 1.2 Antithrombotic Therapy For Chronic Atrial Flutter

Sustained atrial flutter is an unusual arrhythmia since the rhythm usually degenerates to AF or spontaneously reverts to NSR. Many patients with persistent atrial flutter have periods of atrial flutter alternating with periods of AF, a pattern that carries the risk of thromboembolism of AF. There are relatively few data from longitudinal studies assessing risk of thromboembolism with well-documented sustained atrial flutter.

Both mitral valve M-mode and transmitral Doppler studies demonstrate more organized

atrial mechanical function in patients with sustained atrial flutter than in those with AF. A transesophageal echocardiographic study among 19 patients with atrial flutter and 44 patients with AF<sup>184</sup> found that patients with atrial flutter had greater left atrial appendage flow velocities and shear rates compared to those with AF.

TEE evidence of atrial thrombi has been documented in a number of reports of patients with atrial flutter. Two series evaluated patients with atrial flutter for a mean duration of 33 to 36 days who did not have a history of AF, rheumatic heart disease, or a prosthetic heart valve.<sup>185,186</sup> A left atrial thrombus was found in 1–1.6%, a right atrial thrombus in 1% of subjects, and spontaneous left atrial echo contrast in 11–13%.<sup>185,186</sup> Thrombi in atrial flutter may be related to the duration of the arrhythmia. In a TEE study of 30 patients with chronic atrial flutter (duration 6.4 months), 7% of subjects had evidence of left atrial appendage thrombus and 25% had spontaneous echo contrast prior to cardioversion.<sup>187</sup> Finally, a 21% incidence of intra-atrial thrombi was described in 24 patients with atrial flutter undergoing transesophageal echocardiography.<sup>188</sup> However, the majority of these patients were referred for TEE because of a recent neurologic event, indicating an important selection bias. Depressed left ventricular systolic function was more common among those with thrombi, as was spontaneous left atrial contrast.

In addition to echocardiographic evidence of depressed atrial appendage function and atrial thrombi, a retrospective analysis of 100 patients suggests that the risk of stroke in patients with persistent atrial flutter may be higher than previously assumed.<sup>189</sup> This conclusion is supported by the 7% risk of thromboembolism over 26 months of follow-up observed in a study of 191 consecutive unselected patients referred for treatment of atrial flutter.<sup>190</sup> The role of anticoagulant therapy for patients with atrial flutter has not been evaluated in clinical trials, but since these patients are at increased risk of developing AF, it is reasonable to base decisions regarding antithrombotic therapy on the risk stratification schemes used for AF.

#### Recommendation

**1.2. For patients with atrial flutter, we recommend that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (Grade 1C).**

#### 1.3 Valvular Heart Disease and AF

Patients with AF and prosthetic heart valves (both mechanical and tissue valves) or rheumatic mitral

valve disease are at high risk for stroke (see the chapter on “Valvular and Structural Heart Disease” in this supplement).<sup>15</sup> Most of the randomized trials excluded such patients because anticoagulation was strongly believed to be beneficial. The NASPEAF trial<sup>17,64</sup> was notable in that it enrolled patients with mitral stenosis, but such patients were treated with one of two anticoagulation regimens (see above) and none received placebo. We believe that the results of randomized trials in patients without valvular diseases are readily generalizable to patients with valvular disease, including those with prosthetic heart valves. The NASPEAF study<sup>17,64</sup> indicates that INR targeted at 1.9 plus triflusal may be comparable to INR of 2.0 to 3.0, although more data are needed to confirm these results. For AF patients with a mechanical prosthetic heart valve, the INR target may be higher than 2.0 to 3.0, and addition of aspirin may be appropriate depending on the type of mechanical prosthetic heart valve, the position of the prosthesis, and the presence of other risk factors (see the chapter on “Valvular and Structural Heart Disease” in this supplement).

#### Recommendations

**1.3.1. For patients with AF and mitral stenosis, we recommend long-term anticoagulation with an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0) [Grade 1B].**

**1.3.2. For patients with AF and prosthetic heart valves we recommend long-term anticoagulation with an oral VKA, such as warfarin, at an intensity appropriate for the specific type of prosthesis (Grade 1B). See the chapter on “Valvular and Structural Heart Disease” in this supplement.**

#### 1.4 AF Following Cardiac Surgery

AF occurs in 20 to 50% of patients following open-heart surgery,<sup>191,192</sup> depending on definitions and methods of detection. The incidence is 11 to 40% after coronary artery bypass grafting.<sup>191,193,194</sup> Postoperative AF may arise due to increased release of catecholamines, autonomic imbalance, pericardial inflammation, surgical manipulation of the atrium, mobilization of fluids affecting neurohormonal and electrical properties of the atria,<sup>195</sup> or alterations in atrial refractoriness resulting from intraoperative atrial ischemic injury.<sup>196</sup> Patients who acquire AF following CABG surgery often demonstrate hemodynamic instability that requires inotropic support, intra-aortic balloon counterpulsation, or re-operation for bleeding.<sup>194</sup> Postoperative AF usually occurs within the first 5 days of cardiac surgery, with a peak

incidence on day 2. The dysrhythmia usually runs a self-terminating course, and  $\geq 90\%$  of patients have resumed NSR by 6 to 8 weeks after surgery,<sup>197</sup> a rate of spontaneous resolution higher than for AF occurring in other situations. Atrial flutter is less common than AF following cardiac surgery.<sup>198</sup>

Older age is the most reproducible predictor of postoperative AF in patients undergoing cardiac surgery.<sup>199</sup> Other independent predictors include valvular heart disease, chronic lung disease, atrial enlargement, and preoperative atrial arrhythmias. In a multivariate analysis, age 70–80 years, age  $> 80$  years, male gender, hypertension, intra-operative intra-aortic balloon support, post-operative pneumonia, mechanical ventilation for  $> 24$  h, and return to the ICUs predicted AF following CABG surgery.<sup>199</sup> The prediction rule developed by Weber<sup>200</sup> uses age, preoperative  $\beta$ -blocker therapy, left ventricular ejection fraction, and P-wave duration on the ECG in a multivariate prediction scheme. Prospectively, this algorithm identified patients with a 2.9-fold increased risk of AF, with 62% sensitivity and 85% specificity.<sup>200</sup> The P-wave duration on preoperative signal-averaged electrocardiography has independent predictive value for development of postoperative AF in patients undergoing cardiac surgery.<sup>201</sup> Adding intra-operative transesophageal echocardiography (TEE), the combination of age  $\geq 75$  years plus post-cardiopulmonary bypass left upper pulmonary vein systolic/diastolic velocity ratio  $\geq 0.5$  and left atrial appendage area  $\geq 4.0$  cm<sup>2</sup> predicted an 83% probability of developing postoperative AF.<sup>202</sup>

The risk of thromboembolism associated with postoperative AF, particularly ischemic stroke, occurs at a rate of 1 to 6%, and carries a high mortality rate (13 to 41%).<sup>203–206</sup> The risk of thromboembolism increases to almost 9% among patients  $\geq 75$  years of age undergoing CABG surgery.<sup>207–209</sup> Rates of thromboembolism among patients undergoing noncoronary cardiac operations may differ, and have not been studied as extensively as in those undergoing coronary surgery. As more elderly patients undergo cardiac surgery, the problem of postoperative stroke has prompted efforts to develop practical and effective preventive strategies.<sup>210</sup>

When AF persists  $\geq 48$  h in the postoperative period following CABG surgery, anticoagulation with heparin or an oral VKA is appropriate,<sup>207,211</sup> but the potential for bleeding in surgical patients poses a particular challenge. The choice of drug (heparin and/or oral anticoagulant) must be based on the individual clinical situation. Optimal protection against ischemic stroke for high-risk patients with AF involves anticoagulation with an oral VKA, such as warfarin (INR, 2.0 to 3.0). This is associated with a considerable risk of bleeding among the elderly

during the early postoperative period, but no adequate study has specifically addressed the relative efficacy and toxicity in this clinical situation.

Although the left atrial appendage is amenable to ligation, plication, or amputation during cardiac surgery, it is not clear whether these maneuvers reduce the incidence of postoperative thromboembolism, stroke, or the need for anticoagulation,<sup>212–217</sup> and several studies are in progress to evaluate this prospectively. In one study of patients undergoing prosthetic mitral valve replacement, ligation of the left atrial appendage was associated with a reduced rate of ischemic events.<sup>218</sup> Although the majority of the patients in that study had a cardiac rhythm other than sinus (presumably AF or flutter in most), the intensity of anticoagulation was not described, and the performance of LAA obliteration at the time of cardiac operation was not randomized. Ligation was incomplete in 2.9% of cases as assessed by transesophageal echocardiography, and further study will be needed to establish how this might compromise a protective effect.<sup>216</sup> Among other nonpharmacological alternatives under investigation is the use of the surgical Maze procedure in one or another modification to reduce the likelihood that postoperative AF will develop,<sup>196,219</sup> although this is currently performed more often in conjunction with mitral valve surgery.

## Recommendation

**1.4. For patients with AF occurring shortly after open-heart surgery and lasting  $\geq 48$  h, we suggest anticoagulation with an oral VKA, such as warfarin, if bleeding risks are acceptable (Grade 2C). The target INR is 2.5 (range, 2.0 to 3.0). We suggest continuing anticoagulation for 4 weeks following reversion to and maintenance of NSR, particularly if patients have risk factors for thromboembolism (Grade 2C).**

### 2.0. ANTICOAGULATION FOR ELECTIVE CARDIOVERSION OF AF OR ATRIAL FLUTTER

#### 2.1 *Anticoagulation for Elective Cardioversion of AF*

More than four decades have passed since Lown and coworkers<sup>220,221</sup> first introduced synchronized capacitor discharge for the rapid termination of atrial and ventricular tachyarrhythmias. Systemic embolism is the most serious complication of cardioversion and may follow external or internal direct-current (DC), pharmacological, and spontaneous cardioversion of AF. Evidence favoring the efficacy of anticoagulation is based on observational studies.

The large reported efficacy from such studies has prevented trials comparing anticoagulation to a “no anticoagulation” alternative.

Bjerkelund and Orning<sup>222</sup> performed a prospective cohort study in which cardioversion without anticoagulants resulted in a 5.3% incidence of clinical thromboembolism, vs a 0.8% incidence of thromboembolism in patients receiving oral anticoagulants. Although this was not a randomized comparison, the results are compelling because the patients receiving anticoagulants were also at higher risk (many with valvular heart disease) than those who were not anticoagulated. Several authors of case series also favor the use of adjusted-dose anticoagulation before cardioversion.<sup>221,223–226</sup> Although sometimes occurring up to  $\geq 10$  days after cardioversion, most thromboemboli occur during the first 72 h, and are presumed to result from migration of thrombi present within the left atrium at the time of cardioversion.<sup>227</sup> After conversion to NSR, atrial appendage dysfunction may persist or worsen, leading to a prothrombotic state, highlighting the importance of peri-cardioversion anticoagulation (see below). The duration of anticoagulation before cardioversion is not clearly defined since the majority of these studies were retrospective analyses, but many investigators recommend 3 weeks of prophylactic adjusted-dose warfarin (INR, 2.0 to 3.0) before and 4 weeks after cardioversion. TEE data suggest the prevalence of atrial thrombi approaches 10% if patients have a subtherapeutic INR ( $< 2.0$ ) during the 3 weeks prior to cardioversion.<sup>228</sup> The recommendations that follow have been based on clinical observations and data from several of these studies.

Most information on cardioversion-related thromboembolism is based on electrical cardioversion. There are limited clinical data bearing on embolism after pharmacological or spontaneous cardioversion of AF to NSR. Nonetheless, it seems prudent to administer anticoagulation in a similar manner for both pharmacological and electrical conversion. Goldman<sup>229</sup> reported that embolism occurred in 1.5% of 400 patients treated with quinidine for conversion of AF to NSR. This was similar to the 1.2% incidence of embolism that Lown<sup>221</sup> reported in 450 electrical cardioversions. These data are slightly higher than the incidence of clinical thromboembolism after 3 weeks of precardioversion warfarin (INR, 2.0 to 3.0) reported by the prospective and more contemporary Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE)<sup>137</sup> and the Ludwigshafen Observational Cardioversion studies<sup>230</sup> for patients undergoing DC cardioversion. In the ACUTE trial of 603 patients randomly assigned to conventional therapy of 3 weeks of precardiover-

sion anticoagulation with warfarin, 333 underwent DC cardioversion with 3 (0.9%) subsequent neurologic events. During the conventional treatment phase of the Ludwigshafen Observational study, 357 subjects underwent DC cardioversion with 3 (0.8%) neurologic events after successful cardioversion. Retrospective data from Europe<sup>231</sup> suggest there may be a benefit to a slightly higher INR immediately prior to cardioversion, with no embolic complications among 779 attempted cardioversions with an INR  $\geq 2.5$  vs a rate of 0.9% among 756 if the INR was 1.5 to 2.4.

The mechanism of benefit conveyed by the 3 weeks of warfarin prior to elective cardioversion had previously been ascribed to thrombus organization and adherence to the atrial wall.<sup>229</sup> More recently, serial TEE studies among those presenting with new onset AF and atrial thrombi on initial TEE have demonstrated resolution of the thrombi after one month of warfarin in the majority of subjects.<sup>232–234</sup> However, it is likely that thrombi persist in a significant minority.<sup>230</sup> It thus appears that the 3 weeks of warfarin may facilitate both “silent” thrombus resolution and thrombus organization/adherence.

The immediate post-cardioversion period is associated with increased risk for thrombus formation. Utilizing TEE, further depression of left atrial appendage ejection velocities, more intense left atrial spontaneous echocardiographic contrast, and even new thrombus formation have been described after external DC, internal DC, and spontaneous cardioversion.<sup>235–238</sup> These data underscore the importance of therapeutic anticoagulation during the peri-cardioversion period. Following restoration of normal atrial electrical activity on the surface ECG, the mechanical contraction of the body of the left atrium may remain dysfunctional for as long as 2 to 4 weeks after cardioversion.<sup>239–241</sup> Anecdotally, a “fibrillatory” pattern has been found in the appendage with sinus-type activity on the surface ECG and transmitral Doppler spectra.<sup>242</sup> The duration of atrial recovery appears to be directly related to the duration of AF prior to cardioversion.<sup>243,244</sup> For these reasons, adjusted-dose anticoagulation (INR 2.0–3.0) should be continued for at least 4 weeks following cardioversion. In addition to prophylaxis against new thrombus formation during recovery of atrial mechanical activity, warfarin also serves as prophylaxis against thrombus formation should the patient revert to AF.

### 2.1.1 Conventional vs TEE-Guided Cardioversion

For over a decade, an alternative strategy has been suggested for cardioversion of patients with AF of  $> 2$  days or of unknown duration. Among patients

with AF, the vast majority (> 90%) of thrombi are located within, or involve the left atrial appendage.<sup>16,232,233,238,241</sup> While the detection of left atrial appendage thrombi is unreliable using conventional transthoracic echocardiography, biplane and multiplane TEE have demonstrated very high accuracy and therefore offer the opportunity to perform early cardioversion for those in whom no atrial appendage thrombi are observed.<sup>16,245,246</sup> Therapeutic systemic anticoagulation with IV heparin and/or warfarin should still be employed at the time of TEE and cardioversion because of the concern that new thrombus may form during the peri- or post-cardioversion period. Data from several studies<sup>137,232,233,241,245,247</sup> currently suggest rates of thromboembolism that are similar (< 1%) to those associated with standard therapy of 3 weeks of therapeutic warfarin prior to elective cardioversion, with the advantages of an earlier recovery of atrial mechanical function, ease of anticoagulation management, elimination of the need for readmission for elective cardioversion, and of potentially attractive cost-effectiveness if performed expeditiously and without a somewhat redundant transthoracic echo.<sup>248,249</sup> Limited data on silent stroke based on 1-month cerebral MRI using a TEE guided approach suggest a silent stroke risk of 4.7%.<sup>250</sup> Corresponding data for conventional therapy are unknown. Limitations of the TEE approach include patient discomfort and rare procedural complications.

Despite the absence of left atrial appendage thrombi on precardioversion TEE, stroke has been described among patients who did not receive anticoagulation at the time of TEE or continued anticoagulation during the peri-cardioversion period through a full month after cardioversion.<sup>251–254</sup> These adverse events may have occurred because the sensitivity of TEE for small atrial appendage thrombus is not 100%, development of new thrombus because of transient atrial dysfunction during the postcardioversion period, or other mechanisms.

The ACUTE randomized, multicenter, international study enrolled 1222 patients with AF for whom elective electrical cardioversion was planned in order to compare the conventional vs the potentially expedited TEE approach.<sup>137</sup> 619 subjects were randomly assigned to the TEE arm. There were 5 embolic events in the TEE arm vs 3 in the conventional arm (p value not significant). It is worth noting that among those assigned to the TEE arm, only 549 actually had a TEE, including 425 who subsequently underwent DC cardioversion. Among these 425 patients, 4 neurologic events occurred during the first month after cardioversion. Three of these adverse events occurred in patients who had recurrent AF with a subtherapeutic INR (< 2.0), emphasizing

the importance of postcardioversion therapeutic (INR, 2.0 to 3.0) anticoagulation. Among the 603 patients in the conventional anticoagulation regimen arm, only 333 underwent cardioversion after 3 weeks of anticoagulation. Many of the other patients in this arm spontaneously converted to NSR before their scheduled cardioversion. Overall, cardioversion occurred earlier in the TEE-guided group but there was no difference in the likelihood of NSR by 8 weeks (52.7% in the TEE group vs 50.4% in the conventional group; p = 0.43) following randomization (mean, 7 weeks after cardioversion for the TEE arm and 3 weeks for the conventionally treated arm).<sup>137</sup> There was also no statistically significant difference in the likelihood of sinus rhythm at 6 months after study entry.<sup>255</sup> In contrast, another prospective, though nonrandomized study demonstrated lower recurrence of AF and higher likelihood of NSR at 1-year among subjects who undergo TEE guided cardioversion for whom the total duration of AF is < 3 weeks, a period inconsistent with conventional anticoagulation regimens.<sup>256</sup> Current data generally support the use of therapeutic LMWH (full DVT doses) as an alternative to unfractionated heparin prior to and post-cardioversion with regards to protection against post-cardioversion clinical thromboembolism.<sup>257–259</sup> Interestingly, for nonanticoagulated patients, the absence of an atrial thrombus on a prior TEE does not reduce the prevalence of finding an atrial thrombus when the patient presents with another episode of AF.<sup>260</sup>

### 2.1.2 Cardioversion of AF of Known Duration of < 48 h

For AF of short (< 48 h) duration, a common practice is to cardiovert without TEE or prolonged precardioversion anticoagulation. This practice was called into question when a study reported a 13% prevalence of atrial thrombi on TEE among patients with AF of < 72 h duration. Subsequently, data were reported from a study of 357 patients who had a symptomatic duration of AF for < 48 h.<sup>261</sup> Two hundred fifty patients converted spontaneously and 107 underwent pharmacologic or electrical cardioversion, all without screening TEE or 3 weeks of warfarin prior to cardioversion. Clinical thromboembolism occurred in three subjects (< 1%), all of whom were elderly women without a history of prior AF and with normal left ventricular systolic function. Gallagher et al<sup>231</sup> reported on retrospective data regarding 258 patients with AF < 2 days undergoing cardioversion. One (0.5%) embolic event occurred in 198 who did not receive precardioversion or postcardioversion warfarin with no events (0%) among 60 patients who did receive precardioversion and post-

cardioversion warfarin. Though safe in these studies, it may be prudent to initiate heparin anticoagulation and to perform TEE (or delay cardioversion for 1 month) for high-risk patients. Even without use of TEE, anticoagulation with heparin (*eg*, IV heparin with target PTT of 60 s, range 50–70 s or LMWH at full DVT treatment doses) immediately prior to cardioversion may be appropriate. Many of these patients will require anticoagulation after cardioversion should AF recur, and the use of heparin will decrease the risk of thrombus formation during the peri-cardioversion period. There are no randomized trials comparing these approaches in patients with AF of < 48 h duration.

### 2.1.3 Emergency Cardioversion of AF

Emergency cardioversion is performed to terminate atrial tachyarrhythmias with a rapid ventricular response causing angina, heart failure, hypotension, or syncope. In individuals with impaired ventricular function, clinical deterioration may occur within minutes or hours of the onset of the arrhythmia, and urgent electrical or pharmacologic cardioversion is indicated. There are no published data on the use of anticoagulation for emergency cardioversion. Unfractionated heparin or low molecular weight heparin therapy at the time of cardioversion may be useful to prevent thrombi from forming due to further atrial appendage dysfunction after cardioversion. It seems reasonable to continue anticoagulation for 4 weeks using a heparin to warfarin (INR, 2.0 to 3.0) transition.

### 2.1.4 Cardioversion of Atrial Flutter

As with the risk of thromboembolism in persistent atrial flutter, there appears to be an increased risk of clinical thromboembolism among patients referred for elective cardioversion of atrial flutter. Unfortunately, no prospective report has been sufficiently large to accurately define both the risk of embolization and the possible protective effect of anticoagulant therapy. Another confounding factor, as noted above, is that many patients with atrial flutter also have episodes of AF. The safety of performing cardioversion without anticoagulation in atrial flutter was initially suggested by the absence of clinical thromboembolic events in a total of 207 patients from two series who underwent elective cardioversion for atrial flutter without anticoagulation prior to or after cardioversion.<sup>224,262</sup> More recent retrospective data suggest a significant risk of thromboembolism. Gallagher et al<sup>231</sup> retrospectively reviewed data from 222 patients with atrial flutter/atrial tachycardia undergoing cardioversion without warfarin, with 2 confirmed and an additional 2 probable thrombo-

embolic events. Five events occurred among 292 patients who received warfarin pre- and post-cardioversion. Given the retrospective data collection, the event rates may be underestimated. Patients at particularly high risk include those with valvular heart disease, prior thromboembolism, congestive heart failure and left ventricular systolic dysfunction. Several other reports have shown no events among patients receiving pre- and post-cardioversion warfarin therapy.<sup>189,190,263</sup>

As with AF, a transient reduction in atrial mechanical activity (atrial “stunning”) is common after successful cardioversion of atrial flutter although the severity of the depression is less pronounced than for AF.<sup>184,187,264,265</sup> These changes predispose to *de novo* thrombus formation which has been documented in patients with atrial flutter.<sup>266</sup> Collectively, these findings raise concern that patients with atrial flutter are at increased risk of embolization at the time of cardioversion. We recommend treating patients with atrial flutter in the same manner as patients with AF at the time of cardioversion, especially those with a history of AF or with clinical features that are associated with high risk of stroke in AF.<sup>264,267</sup>

## 2.2 Rate vs Rhythm Control in AF: Implications for Use of Anticoagulants

The previous sections address strategies for cardioversion of AF to NSR. Before the publication of major trials discussed below, most physicians preferred cardioversion and rhythm control to rate control for patients with AF of recent onset. This was based on the presumption that restoration of NSR would reduce or avoid the adverse consequences resulting from reduction of cardiac output, persistent tachycardia, and atrial thrombus formation that can lead to systemic embolism. With this approach, anticoagulation was sometimes stopped one month after apparently successful cardioversion when NSR seemed sustained, based on the assumption that restoration of NSR removed the risk of thromboembolism attributable to AF. Two randomized trials, the AFFIRM<sup>268</sup> and the RACE<sup>269</sup> trials demonstrated that ischemic events occurred with equal frequency regardless of whether a rate control or rhythm control strategy was pursued, and occurred most often after warfarin had been stopped or when the INR was subtherapeutic. These findings indicate that high-risk patients in whom NSR is restored still require chronic warfarin anticoagulation.

There are at least two likely explanations for the failure of rhythm control to reduce embolic risk: (1) Despite successful cardioversion and antiarrhythmic drug therapy, the rate of recurrent AF is 40 to 60% at 1 year<sup>270,271</sup>; many episodes of recurrent AF are

not symptomatic and may be undiagnosed if paroxysmal<sup>145,146</sup>; during these asymptomatic periods of AF, thrombi may form which can cause clinical thromboembolism; and (2) patients with AF not associated with reversible disease (*eg*, hyperthyroidism) often have other factors predisposing to thromboembolism despite maintenance of NSR. These include complex atheromatous aortic plaque and left ventricular dysfunction.<sup>113,136</sup>

Rate control does not require chronic administration of antiarrhythmic drugs, but it may perpetuate the suboptimal hemodynamics that can contribute to symptoms of fatigue or dyspnea in some patients with AF. In addition, adequate rate control with pharmacologic therapy is occasionally difficult to achieve, requiring nonpharmacologic approaches, particularly radiofrequency ablation of the AV node and pacemaker insertion.

Three randomized trials have compared rhythm and rate control approaches. Each gave similar results, showing equivalent outcomes in both arms, with the predominance of thromboembolic events among patients not receiving warfarin at a dose sufficient to maintain the INR in the target range.<sup>268,269</sup> The largest trial, AFFIRM, included 4,060 patients with recurrent AF.<sup>268</sup> Study subjects were > 65 years old or had other risk factors for stroke or death and no contraindications to anticoagulation therapy. All patients were initially anticoagulated, but warfarin could be withdrawn from those in the rhythm control arm who maintained NSR. At 5 years, 35% of rate control patients were in NSR compared to 63% of those in the rhythm control group. Over 85% of patients in the rate control arm were treated with warfarin as compared to 70% in the rhythm control arm. After a mean follow-up of 3.5 years, all-cause mortality (the primary end point) was not reduced by rhythm control (26.7% vs 25.9%, rhythm control group vs rate control groups, respectively;  $p = 0.08$ ) and there was a trend toward a higher risk of ischemic stroke (7.1% with rhythm control vs 5.5% for rate control;  $p = 0.79$ ). Importantly, 72% of strokes occurred in patients receiving no warfarin or with INR < 2.0. There was no significant difference in functional status or quality of life in the two groups.

The RACE trial enrolled 522 patients with recurrent AF or atrial flutter < 1 year in duration who underwent cardioversion on one or two occasions within the prior two years.<sup>269</sup> Patients were randomly assigned to rate control or to rhythm control strategies. The primary outcome was a composite of death from cardiovascular causes, heart failure, thromboembolism, bleeding, implantation of a pacemaker, and severe adverse

effects of drugs. After a 2.3-year follow-up, there was a trend toward a lower incidence of the primary end point with rate control (17.2% vs 22.6% with rhythm control; hazard ratio, 0.73; 90% CI, 0.53 to 1.01) with no difference in cardiovascular mortality (6.8% vs 7%). There was also a trend toward a higher incidence of nonfatal end points among patients assigned to the rhythm control treatments. In a subset analysis, patients with hypertension randomly assigned to rhythm control had a significantly higher incidence of the primary end point (30.8% vs 17.3% for rate control); there was no difference in normotensive patients. There was a higher incidence of the primary end point among women assigned to rhythm control (32.0% vs 10.5%); there was no difference observed among men.

In the PIAF trial,<sup>272</sup> 252 patients with AF of 7 to 360 days in duration were randomly assigned to rate control with diltiazem or rhythm control with amiodarone. All received anticoagulation with oral VKAs for the duration of the trial. After 1 year, there was no difference in the quality of life between the two groups; patients in the rhythm control group had better exercise tolerance but more frequently required hospitalization.

The data from these trials suggest that both rate and rhythm control approaches are acceptable. However, the larger and longer AFFIRM and RACE studies showed a trend toward fewer primary outcome events with rate control, raising questions as to the overall benefit of vigorous measures to restore and maintain NSR.

Given that ischemic strokes occur despite a rhythm control strategy that results in apparent NSR, it seems prudent to use antithrombotic agents as though AF persisted. In particular, regardless of whether a rate control or rhythm control strategy is chosen, patients with AF at increased risk for stroke should be chronically anticoagulated with an oral VKA such as warfarin to a target INR of 2.5, range 2.0 to 3.0. There is some early evidence that patients with lower burdens of AF may be at decreased risk of stroke compared to those with greater frequency and duration of AF episodes.<sup>148,150</sup> Implanted cardiac devices with recording capacity should allow reliable and quantitative correlation of AF burden and stroke risk.<sup>149</sup> Such studies are underway.<sup>273,274</sup> Results may suggest which patients in apparent NSR can safely forego antithrombotic therapy.

## Recommendations

**2.1.1. For patients with AF of  $\geq 48$  h or of unknown duration for whom pharmacologic or electrical cardioversion is planned, we recommend anticoagulation with an oral VKA, such as**

warfarin, at a target INR of 2.5 (range, 2.0 to 3.0) for 3 weeks before elective cardioversion and for at least 4 weeks after sinus rhythm has been maintained (Grade 1C).

Remark: This recommendation applies to all patients with AF, including those whose risk factor status would otherwise indicate a low risk for stroke. Patients with risk factors for thromboembolism should continue anticoagulation beyond 4 weeks unless there is convincing evidence that sinus rhythm is maintained. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

**2.1.2. For patients with AF of  $\geq 48$  h or of unknown duration who are undergoing pharmacologic or electrical cardioversion, we recommend either immediate anticoagulation with IV unfractionated heparin (target PTT, 60 s; range, 50 to 70 s), or low-molecular-weight heparin (at full DVT treatment doses), or at least 5 days of warfarin (target INR of 2.5; range, 2.0 to 3.0) at the time of cardioversion and performance of a screening multiplane TEE. If no thrombus is seen, cardioversion is successful, and sinus rhythm is maintained, we recommend anticoagulation (target INR, 2.5; range, 2.0 to 3.0) for at least 4 weeks. If a thrombus is seen on TEE, then cardioversion should be postponed and anticoagulation should be continued indefinitely. We recommend obtaining a repeat TEE before attempting later cardioversion** (all Grade 1B addressing the equivalence of TEE-guided vs nonTEE-guided cardioversion; see Recommendation 2.1.1, above).

Remark: The utility of the conventional and TEE-guided approaches is likely comparable. This recommendation applies to all patients with AF, including those whose risk factor status would otherwise indicate a low risk for stroke. Patients with risk factors for thromboembolism should continue anticoagulation beyond 4 weeks unless there is convincing evidence that sinus rhythm is maintained. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

**2.1.3. For patients with AF of known duration < 48 h, we suggest that cardioversion be performed without prolonged anticoagulation** (Grade 2C). **However, in patients without contraindications to anticoagulation, we suggest beginning IV heparin (target PTT, 60 s; range, 50 to 70 s) or LMWH (at full DVT treatment doses) at presentation** (Grade 2C).

Remark: For patients with risk factors for stroke, it is particularly important to be confident that the duration of AF is < 48 h. In such patients with risk factors, a TEE-guided approach (see 2.1.2, above) is

a reasonable alternative strategy. Postcardioversion anticoagulation is based on whether the patient has experienced more than one episode of AF and on his or her risk factor status. For patients with recurrent episodes of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

**2.1.4. For emergency cardioversion in the hemodynamically unstable patient, we suggest that IV unfractionated heparin (target PTT of 60 s with a target range of 50 to 70 s) or low-molecular-weight heparin (at full DVT treatment doses) be started as soon as possible, followed by at least 4 weeks of anticoagulation with an oral VKA, such as warfarin (target INR of 2.5; range, 2.0 to 3.0) if cardioversion is successful and sinus rhythm is maintained** (Grade 2C).

Remark: Long-term continuation of anticoagulation is based on whether the patient has experienced more than one episode of AF and on his or her risk factor status. For patients experiencing more than one episode of AF, Recommendations 1.1.1, 1.1.2, 1.1.3, and 1.1.4 apply.

**2.1.5. For cardioversion of patients with atrial flutter, we suggest use of anticoagulants in the same way as for cardioversion of patients with AF** (Grade 2C).

### 3.0. ANTICOAGULATION IN PATIENTS WITH AF UNDERGOING ELECTROPHYSIOLOGIC INTERVENTIONS

Nonpharmacological measures (*eg*, arrhythmia surgery, ablation techniques) play an increasing role in AF management, and in some instances, offer the possibility of a 'cure' especially where AF is due to pulmonary vein foci.<sup>275,276</sup> However, recurrence rates are still high with catheter ablation techniques. For example, at the 6-month follow-up period, only 54% and 82% of patients remained free of arrhythmia-related symptoms after circumferential pulmonary vein ablation and after segmental pulmonary vein ablation, respectively<sup>277</sup> with a clear relation to center expertise and follow-up duration.<sup>278</sup> Also, asymptomatic episodes do occur and may be increased after catheter ablation, especially among previously symptomatic patients. Clinical follow-up based on symptoms only would substantially overestimate the success rate of ablation procedures.<sup>279</sup> More intense monitoring will identify more (asymptomatic) AF recurrences than simply relying on 12-lead ECG readings at follow-up visits.<sup>279</sup> This is a rapidly evolving field. For the time being, patients with stroke risk factors should continue on anticoagulation following AF surgery

or ablation procedures for a prolonged period to assure no recurrence of AF.

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