Antithrombotic Therapy in Atrial Fibrillation

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

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This chapter about antithrombotic therapy in atrial fibrillation (AF) is part of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading see Guyatt et al, *CHEST 2004; 126:179S–187S*). 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 to 3.0): In patients with persistent or paroxysmal AF (PAF) [intermittent AF] at high risk of stroke (*ie*, having any of the following features: prior ischemic stroke, transient ischemic attack, or systemic embolism, age > 75 years, moderately or severely impaired left ventricular systolic function and/or congestive heart failure, history of hypertension, or diabetes mellitus), we recommend anticoagulation with an oral VKA, such as warfarin (Grade 1A). In patients with persistent AF or PAF, age 65 to 75 years, in the absence of other risk factors, we recommend antithrombotic therapy with either an oral VKA or aspirin, 325 mg/d, in this group of patients who are at intermediate risk of stroke (Grade 1A). In patients with persistent AF or PAF < 65 years old and with no other risk factors, we recommend aspirin, 325 mg/d (Grade 1B). For patients with AF and mitral stenosis, we recommend anticoagulation with an oral VKA (Grade 1C+). For patients with AF and prosthetic heart valves, we recommend anticoagulation with an oral VKA (Grade 1C+); the target INR may be increased and aspirin added depending on valve type and position, and on patient factors. 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 for 3 weeks before and for at least 4 weeks after successful cardioversion (Grade 1C+). For patients with AF of ≥ 48 h or of unknown duration undergoing pharmacologic or electrical cardioversion, an alternative strategy is anticoagulation and screening multiplane transesophageal echocardiography (Grade 1B). If no thrombus is seen and cardioversion is successful, we recommend anticoagulation for at least 4 weeks (Grade 1B). For patients with AF of known duration < 48 h, we suggest cardioversion without anticoagulation (Grade 2C). However, in patients without contraindications to anticoagulation, we suggest beginning IV heparin or low molecular weight heparin at presentation (Grade 2C).

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

Abbreviations: ACCP = American College of Chest Physicians; ACUTE = Assessment of Cardioversion Using Transephageal Echocardiography; AF = atrial fibrillation; AFASAK = Atrial Fibrillation, Aspirin and Anticoagulation; AFI = Atrial Fibrillation Investigators; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CABG = Coronary Artery Bypass Grafting surgery; CAFA = Canadian Atrial Fibrillation Anticoagulation; $CHADS_2$ = Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke (Doubled); 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; ICH = intracranial hemorrhage; INR = international normalized ratio; LASAF = Low-Dose Aspirin, Stroke, and Atrial Fibrillation; LMWH = low molecular weight heparin; MI = myocardial infarction; NASPEAF = National Study for Prevention of Embolism in Atrial Fibrillation; NNT = number needed to treat for 1 year; NSR = normal sinus rhythm; OAC = oral anticoagulation with vitamin K antagonists; PAF = paroxysmal atrial fibrillation; PATAF = Primary Prevention of Arterial Thromboembolism in Nonrheumatic AF in Primary Care Trial; PT = prothrombin time; PTR = prothrombin time ratio; PTT = partial thromboplastin time; RACE = Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation Study; RR = relative risk; RRR = relative risk reduction; SPAF = Stroke Prevention in Atrial Fibrillation; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation; SPORTIF = Stroke Prevention Using an Oral Thrombin Inhibitor in Patients with AF; TEE = transesophageal echocardiography; TIA = transient ischemic attack

A trial 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.[1,2] 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.[1–5] The median age of patients with AF is approximately 72 years. AF is more prevalent in men than in women at all ages.[1,3–5] Because of the projected aging of the US population, the number of individuals with AF is likely to increase substantially in coming decades.[1]

The rate of ischemic stroke among patients with AF included in primary prevention clinical trials and not treated with antithrombotic therapy averaged 4.5%/yr, similar to estimates of stroke risk from the Framingham Heart Study.[6,7] AF increases the risk of stroke fourfold to

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fivefold across all age groups. As a consequence of its increasing prevalence, AF becomes an increasingly important cause of stroke with advancing age. In the Framingham Study, the 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.[8] Overall, AF accounts for approximately 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,[9] by extension of operative findings of intracardiac thrombus in patients with rheumatic mitral valve disease,[10] and more recently by transesophageal echocardiography (TEE) of the thrombus in the left atrium of patients with AF, mainly in the left atrial appendage.[11] 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. Further discussion of management of antithrombotic therapy in patients with AF and these latter conditions is presented in the chapters on valvular heart disease and prosthetic heart valves. 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.

1.0 Long-term Antithrombotic Therapy for Chronic AF or Atrial Flutter: Anticoagulants and Antiplatelet Agents

1.1 Chronic AF

Efficacy of oral anticoagulant therapy

Results of a systematic review of randomized trials of oral vitamin K antagonist (VKA) therapy vs no antithrombotic therapy: Investigators from the five primary preven-

Table 1—*Question Definition and Eligibility Criteria for Antithrombotic Therapy in AF Studies

Section	Conditions	Intervention or Exposure	Outcomes/Safety	Methodology	Exclusion Criteria†
1.1	Chronic 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 patients were included, although individual studies vary.
1.2	Chronic 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 oral anticoagulation	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

*RCT = randomized controlled trial.

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

tion trials pooled their data after standardizing clinical definitions.[6] The individual studies and their results are summarized in Tables 2–5.[12–16] The results of individual-subject meta-analyses of these trials and later trials with pooled data are provided in Table 6. The clinical trials included patients with chronic persistent (also known as "sustained," and including the category "permanent"[17]) or, less commonly, paroxysmal AF (PAF) [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 Canadian Atrial Fibrillation Anticoagulation [CAFA] trial[16] was stopped early because of the superiority of anticoagulation seen in other trials). 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 to 1.4% for the patients assigned to adjusted-dose warfarin. The efficacy of warfarin was consistent across studies with an overall relative risk reduction (RRR) of 68% (95% confidence interval [CI], 50 to 79%). The absolute risk reduction implies that 31 ischemic strokes will be prevented each year for every 1,000 patients treated (or patients needed to treat [NNT] for 1 year to prevent 1 stroke = 32) [Table 6].

The percentage of strokes classified as moderate, severe, or fatal ranged between 43% and 64%. Anticoagulation was effective for preventing strokes of all severities. The effect of warfarin was consistent across all patient subgroups. The majority of strokes occurring 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],[18,19] which enrolled only patients with a transient ischemic attack (TIA) or minor stroke within the previous 3 months, the RRR 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). In five of the studies (EAFT,[19] 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%).[6] Overall, the evidence for the efficacy of anticoagulation in AF is strong, consistent, and based on high-quality studies.

In these trials, anticoagulation proved adequately safe, particularly with INR targets of ≤ 3.0. There was no significant increase in major bleeding events in patients treated with adjusted-dose anticoagulation in any of the

Table 2—*AF Trials: No. of Subjects, Follow-up, and Primary Outcome Measures

Study	Year of Publication	Total No. of Patients	No. of Treatment Arms	Mean Follow-up, yr	Primary Outcome Measure
AFASAK 1[12]	1989	1,007	3	1.2	S, SE, TIA, ICH
BAATAF[13]	1990	420	2	2.2	S
SPAF I[14]	1991	1,330	3	1.3	S, SE
CAFA[16]	1991	383	2	1.3	S, SE, ICH, FH
SPINAF[15]	1992	525	2	1.8	S
EAFT[19]	1993	1,007	3	2.3	S, SE, MI, VD, ICH
SPAF II[20]	1994	1,100	2	2.7	S, SE
SPAF III[22]	1996	1,044	2	1.1	S, SE
SIFA[42]	1997	916	2	1.0	S, SE, MI, VD, PE, ICH
ESPS 2[28,29]	1997	429‡	4	1.1	S
AFASAK 2[30]	1998	677	4	NA	S, SE, ICH
Pengo et al[43]	1998	303	2	1.2	S, SE, ICH, FH, VD
LASAF[31]†	1999	285	3	1.5	S, ICH
PATAF[36]	1999	729	3	2.7	S, SE, MH, VD
Japanese NVAF secondary prevention[198]	2000	115	2	1.8	S, SE, TIA
FFAACS[45]	2001	157	2	0.8	S, SE, MI, ICH, VD
NASPEAF[46]	2002‖				
Higher risk		495	2	2.9§	S, SE, TIA, ICH, VD
Lower risk		714	3	2.6§	S, SE, TIA, ICH, VD
SPORTIF III[60]	2003	3,410	2	1.45	S, SE, ICH
SPORTIF V[61]	2003‖	3,922	2	1.67	S, SE, ICH

*S = ischemic stroke; SE = non-CNS systemic embolus; MH = major hemorrhage; FH = fatal hemorrhage; VD = vascular death; PE = pulmonary embolism; NVAF = nonvalvular atrial fibrillation; SIFA = Studio Italiano Fibrillazione Atriale; NA = not available.

†Primary outcome not specified; however, sample size calculated using ischemic stroke plus ICH.

‡This represents only the patients in ESPS 2 with AF.

§Median.

‖Published in abstract form only.

Table 3—*AF Trials: Therapies Tested

Study	Control	Full-Dose OAC, INR Range	Aspirin, mg/d	OAC Plus Aspirin	Low-Dose OAC
AFASAK 1[12]	Yes	2.8–4.2	75		
SPAF I[14]	Yes	2.0–4.5†	325		
BAATAF[13]	Yes	1.5–2.7†			
CAFA[16]	Yes	2.0–3.0			
SPINAF[15]	Yes	1.4–2.8†			
EAFT[19]	Yes	2.5–4.0	300		
SPAF II[20]		2.0–4.5	325		
SPAF III[22] (high risk)		2.0–3.0		325 mg aspirin plus warfarin (INR 1.2–1.5)	
AFASAK 2[30]		2.0–3.0	300	300 ASA plus warfarin, 1.25 mg	Warfarin, 1.25 mg
ESPS 2[28,29]‡	Yes		50		
SIFA[42]		2.0–3.5	400§		
LASAF[31]	Yes		125; 62.5‖		
Pengo et al[43]		2.0–3.0			Warfarin, 1.25 mg
PATAF[36]		2.5–3.5	150		INR 1.1–1.6
Japanese study[198]		2.2–3.5			Warfarin, INR 1.5–2.1
FFAACS[45]		2.0–2.6		Fluindione plus 100 mg ASA	
NASPEAF[46]					
Higher risk		2.0–3.0		Triflusal, 600 mg, plus acenocoumarol, INR 1.4–2.4	
Lower risk		2.0–3.0	Triflusal 600 mg	Triflusal, 600 mg, plus acenocoumar, INR 1.25–2.0	
SPORTIF III[60]		2.0–3.0	Ximelagatran, 36 mg bid		
SPORTIF V[61]		2.0–3.0	Ximelagatran, 36 mg bid		

*ASA = acetylsalicylic acid. See Table 2 for expansion of abbreviation.

†PTR-based target range; INR is estimated.

‡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.

§Indobufen, 200 mg bid (not aspirin).

‖LASAF evaluated two doses of aspirin: 125 mg qd and 125 mg every other day.

randomized trials compared with control subjects (Table 5). 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 control subjects compared to 0.3% in warfarin users.[6]

Description of individual studies: There have been six randomized trials[12–16,19] comparing oral anticoagulation with no antithrombotic treatment in patients with AF: 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[19] (Tables 2–6).

These trials had notable differences in study design. First, warfarin was the oral anticoagulant used in all these trials except for the EAFT,[19] which used phenprocoumon or acenocoumarol. Second, the target intensity of anticoagulation differed. The CAFA trial,[16] the Atrial Fibrillation, Aspirin and Anticoagulation (AFASAK) trial,[12] and EAFT used INR target levels of 2.0 to 3.0, 2.8 to 4.2, and 2.5 to 4.0, respectively. The US-based trials used the less standardized PTRs: the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)[13] and the Stroke Prevention in Atrial Fibrillation (SPINAF) trial[15] had a target of PTR of 1.2 to 1.5, while the first Stroke Prevention in Atrial Fibrillation (SPAF) study[14] used a PTR of 1.3 to 1.8. The INR equivalent of these PTR targets in the American trials has been roughly estimated as 1.4 to 2.8 for BAATAF[13] and SPINAF,[15] and 2.0 to 4.5 for SPAF I[20] (Table 3). Third, SPINAF[15] and CAFA[16] were blinded trials, while the others were open-label trials. Fourth, in BAATAF,[13] the control group did not receive anticoagulation but could choose to receive 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, 5). All studies considered 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[13] investigators were different: intracranial bleeding, fatal bleeding, or bleeding leading to transfusion of $\geq$ 4 U of blood within 48 h.

Table 4—*AF Trials: Primary Outcome Event Rates

Variables	Annual Rate per 100		RRR, %¶	Reported p Values
OAC vs Control	OAC	Control		
AFASAK 1[12]†	2.7	6.2	56	< 0.05
SPAF I[14]	2.3	7.4	67	0.01
BAATAF[13]	0.4	3.0	86	0.002
CAFA[16]	3.4	4.6	26	0.25
SPINAF[15]	0.9	4.3	79	0.001
EAFT[19]	8.5	16.5	47	0.001
Aspirin vs control	Aspirin	Control		
AFASAK 1[12]†	5.2	6.2	16	NS
SPAF I[14]	3.6	6.3	42	0.02
EAFT[19]	15.5	19.0	17	0.12
ESPS 2[28,29]‡	13.8	20.7	33	0.16
LASAF[31]				
125 mg qd	2.6	2.2	(15)	NS
125 mg every other day	0.7	2.2	68	0.05
OAC vs Aspirin	OAC	Aspirin		
AFASAK 1[12]†	2.7	5.2	48	< 0.05
SPAF II[20]				
≤ 75	1.3	1.9	33	0.24
> 75	3.6	4.8	27	0.39
EAFT[19]	NA	NA	40	0.008
AFASAK 2[30]	3.4	2.7	(21)	NS
PATAF[36]	2.5	3.1	19	NS
OAC vs Low-dose OAC plus aspirin	OAC	OAC plus aspirin		
SPAF III[22]	1.9	7.9	74	< 0.0001
AFASAK 2[30]	3.4	3.2	(6)	NS
NASPEAF (triflusal, not aspirin)[46]§				
Higher risk	4.6	2.3	(50)	0.03
Lower risk	2.5	0.92	(63)	0.04
OAC vs low-dose OAC	OAC	Low-dose OAC		
AFASAK 2[30]	3.4	3.9	13	NS
PATAF[36]	2.5	2.2	(12)	NS
Pengo et al[43]	3.6	6.2	42	0.29
Japanese study[198]	1.1	1.7	35	NS
OAC vs Indobufen	OAC	Indobufen		
SIFA[42]	9.0	10.6	15	NS
OAC vs OAC plus aspirin	OAC	OAC plus aspirin		
FFAACS[45]	2.9	7.9	63	0.21
OAC vs ximelagatran	OAC	Ximelagatran		
SPORTIF III[60]	2.3	1.6	(30)	‖
SPORTIF V[61]	1.2	1.6	25	‖

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

†Based on intention-to-treat analysis.[73]

‡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.[59,198]

¶RRR is given in parenthesis when the risk is reduced by the non-OAC comparator.

Risk of ICH during anticoagulation

A general discussion of the hemorrhagic complications of anticoagulants is covered in the chapter by Levine 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 the ischemic strokes antithrombotic therapy is designed to prevent. Overall, the rates of ICH were reassuringly low in the initial AF randomized trials comparing anticoagulation with control or placebo (Table 5). However, a substantially higher rate of ICH was observed in the SPAF II study,[20] with seven ICHs observed among 385 patients > 75 years old for an annualized rate of 1.8%, compared with 0.8% in patients receiving aspirin. In contrast, in the primary prevention trials, the rate of ICH was only 0.3%/yr among those > 75 years old.[21] In the secondary prevention EAFT study,[19] 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.[18,19] In the high-risk arm of SPAF III,[22] (mean age, 71 years; mean INR, 2.4), the

Table 5—*AF Trials: Rates of Major Bleeding

Variables	All Major Hemorrhage, Annual Rate per 100		ICH, Annual Rate per 100	
OAC vs control	OAC	Control	OAC	Control
AFASAK 1[12]	0.6	0.0	0.3	0
SPAF I[14]	1.5	1.6	0.8	0.8
BAATAF[13]†	0.4	0.2	0.2	0
CAFA[16]	2.1	0.4	0.4	0
SPINAF[15]	1.3	0.9	0	0
EAFT[19]	2.6	0.7	0	0.2
Aspirin vs control	Aspirin	Control	Aspirin	Control
AFASAK 1[12]	0.3	0.0	0	0
SPAF I[14]	1.4	1.9	0.3	0.3
EAFT[19]	0.7	0.6	0.2	0.1
ESPS 2[28,29]‡	0.9	0.4	NA	NA
LASAF[31]§				
125 mg qd	NA	NA	NA	NA
125 mg every other day	NA	NA	NA	NA
OAC vs aspirin	OAC	Aspirin	OAC	Aspirin
AFASAK 1[12]	0.6	0.3	0.3	0
SPAF I[14]	NA	NA	NA	NA
SPAF II[20]				
≤ 75	1.7	0.9	0.5	0.2
> 75	4.2	1.6	1.8	0.8
AFASAK 2[30]	1.7	1.6	0.6	0.3
PATAF[36]	0.2	0.3	0.2	0.3
OAC vs aspirin plus low-dose OAC	OAC	Aspirin plus OAC	OAC	Aspirin plus OAC
SPAF III[22]	2.1	2.4	0.5	0.9
AFASAK 2[30]	1.7	0.3	0.6	0
NASPEAF (triflusal, not aspirin)[46]				
Higher risk	2.1	2.1	0.8	0.3
Lower risk‖	1.8	0.9	0.7	0.2
OAC vs low-dose OAC	OAC	Low-dose OAC	OAC	Low-dose OAC
AFASAK 2[30]	1.1	0.8	0.6	0.3
PATAF[36]	0.2	0.3	0.2	0.3
Pengo et al[43]	2.6	1.0	0.5	0
Japanese study[198]	6.6	0.0	1.1	0.0
OAC vs indobufen	OAC	Indobufen	OAC	Indobufen
SIFA[42]	0.9	0	0	0
OAC vs OAC plus aspirin				
FFAACS[45]	1.4	4.8	NA	NA
OAC vs ximelagatran	OAC	Ximelagatran	OAC	Ximelagatran
SPORTIF III[60]	1.8	1.3	0.4	0.2
SPORTIF V[61]	¶	¶	¶	¶

*See Tables 2, 4 for expansion of abbreviations. Major Hemorrhage includes ICHs and other major hemorrhages. ICHs include both intraparenchymal hemorrhages and subdural hematomas.

†BAATAF criteria for serious bleeding were different from those in other trials (see text).

‡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.

§One fatal hemorrhagic stroke in aspirin, 125 mg qd, group but nonfatal ICH and major non-CNS bleeds not reported.

‖NASPEAF lower-risk group treated with triflusal 600, mg/d, alone experienced annual rates of 0.35 per 100 for all severe bleeds and for ICH.

¶Specific rates not given in abstract, but text states that there was no significant difference in major bleeding or in hemorrhagic stroke.[61]

rate of ICH was 0.5%/yr, compared to a rate of 0.9%/yr in the aspirin plus low-dose warfarin arm. The AFASAK 2 study[23] 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%/yr rates in the three other treatment arms during a shorter period of follow-up.

The reasons for the high ICH rate in the SPAF II trial[24] in patients > 75 years 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). The importance of high INR levels in increasing the risk of ICH was further reinforced by the Stroke Prevention in Reversible Ischemia Trial,[25] a non-AF secondary stroke prevention trial that used an INR target intensity of 3.0 to 4.5. In the Stroke Prevention in Reversible Ischemia Trial,[25] the annual rate of ICH was > 3% among patients treated with anticoagulants. This rate was strongly related to INR values, particularly INR > 4.0.

While ICHs are crucial events, they occurred at such a

Table 6—*Patient-Level Meta-analyses of the Efficacy of Antithrombotic Therapies in AF From Pooled Data of Randomized Trials*

Treatment Comparisons	RRR* (95% CI), %
Adjusted-dose oral anticoagulation vs no antithrombotic therapy[6]	68 (50–79)
Aspirin vs no antithrombotic therapy[32]	21 (0–38)
Adjusted-dose oral anticoagulation vs aspirin[37]	52 (37–63)

*Outcome is ischemic stroke; note that trials involved in each analysis are not identical.

low rate that the individual and the aggregated AF trials observed only a small number of such events. As a consequence, these randomized trials have not been a rich source of information on the determinants of ICH. By contrast, observational studies from large medical centers or anticoagulation clinics can accumulate informative numbers of ICHs on anticoagulation. These studies reveal a dramatic increase in the risk of ICH at INR values > 4.0,[26,27] although 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.[26]

Efficacy of aspirin vs placebo

Results of systematic reviews of aspirin vs no aspirin: The evidence supporting the efficacy of aspirin is substantially weaker than the evidence supporting warfarin. Five studies[12,14,19,28–31] compared aspirin with control. An individual patient-level meta-analysis[32] pooling data from AFASAK 1, SPAF I, and EAFT trials resulted in an estimated RRR of 21% compared to placebo. The associated CI ranged from 0 to 38% RRR, indicating results at the cusp of statistical significance (Table 6).[32] In addition to the pooled patient-level analysis described above, there have been two study-level meta-analyses of aspirin vs control in patients with AF. The first meta-analysis[33] found a 22% (95% CI, 2 to 38%) reduction in the risk of stroke. The second meta-analysis[34] 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 CIs: RRR = 24% (95% CI, − 33 to + 66%).

Description of individual studies: Four of the five trials were placebo controlled, and one study had a nontreatment control.[31] The dose of aspirin varied between 50 mg/d[31] and 325 mg/d.[14] Three of the original trials of oral anticoagulation with VKAs (OAC) included aspirin arms: AFASAK 1 (75 mg/d),[12] SPAF I (325 mg/d),[14] and EAFT (300 mg/d).[19] Aspirin was not statistically significantly more effective than placebo in AFASAK 1[12] and EAFT.[19] Evidence of aspirin efficacy comes mainly from the SPAF I trial,[14] in which a statistically significant 42% RRR was reported. SPAF I[14] 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 RRR afforded by aspirin was a highly significant 94%, while in the second cohort the comparable RRR was an insignificant 8%, similar in magnitude to the effect found in AFASAK 1[12] and EAFT.[19] The Low-Dose Aspirin, Stroke, and Atrial Fibrillation (LASAF) study[31] reported inconsistent effects of aspirin in its two component trials (125 mg/d vs control and 125 mg every other day vs control). Data from other trials also bear on the efficacy of aspirin. The European Stroke Prevention Study (ESPS)-2 was a large trial[28] 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[29] reported a nonsignificant 33% RRR vs placebo. The BAATAF trial[35] 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.

Efficacy of oral anticoagulant therapy vs aspirin

Systematic reviews of randomized trials of warfarin vs aspirin: Six studies[12,19,20,30,36] compared oral VKAs directly with aspirin (Table 3). Overall, these results suggest that the risk reduction associated with oral VKA therapy is considerably greater than that provided by aspirin. A metaanalysis[33] reported a 36% (95% CI, 14 to 52%) relative reduction in the risk of all stroke with adjusted-dose oral anticoagulation compared with aspirin, and a 46% (95% CI, 27 to 60%) reduction in the risk of ischemic stroke. The difference between the two analyses was largely due to the increased rate of ICH in the SPAF II study,[20] in which the target INR range (2.0 to 4.5) extended well above currently recommended intensities. Probably the highest-quality assessment of currently available data was the patient-level meta-analysis[37] from the AFASAK 1 and 2, EAFT, Primary Prevention of Arterial Thromboembolism in Nonrheumatic AF in Primary Care Trial (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 6). Major hemorrhage was increased 1.7-fold (95% CI for hazard ratio,1.21 to 2.41). On balance, treating 1,000 patients with AF for 1 year with adjusted-dose oral anticoagulants rather than aspirin would avoid 23 ischemic strokes while causing nine additional major bleeds. The SPAF III and AFASAK 2 trial results were included in this pooled analysis, 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.

Description of individual studies: The SPAF II trial[20] included two separate trials, one for individuals aged ≤ 75 years, and one for those > 75 years old (Table 3). 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. The SPAF II study[20] included the experience of patients who had

participated in group 1 of SPAF I,[14] in which aspirin-treated patients had an extremely low event rate; moreover, 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,[22] 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 ≤ 3 mg) plus aspirin (325 mg/d), or adjusted-dose warfarin (target INR, 2.0 to 3.0). AFASAK 2[30] randomized patients to warfarin, 1.25 mg/d, and aspirin, 300 mg/d, or adjusted-dose warfarin (target INR, 2.0 to 3.0).

In AFASAK 1[12] and EAFT,[19] adjusted-dose warfarin decreased the risk of primary events by 48% and 40%, respectively, compared with aspirin (both results were statistically significant). The SPAF III high-risk study[22] found a marked superiority of adjusted-dose warfarin (INR, 2.0 to 3.0) over low-dose warfarin plus aspirin (RRR = 74%). AFASAK 2[30] 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). The trial was stopped about midway through the planned enrollment, in part because of the results of SPAF III.[22] 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[36] 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 4, 5).

Effects on stroke severity

While analyses have emphasized the efficacy of antithrombotic agents in reducing the risk of all ischemic stroke, it appears that oral VKA therapy has the specific advantage of preventing severe strokes. This effect was observed in the SPAF studies[38,39] and ascribed to better prevention of cardioembolic strokes. Meta-analyses indicate that the efficacy of aspirin compared to placebo diminishes from 22% for all stroke to 13% (95% CI, − 19 to 36%) for disabling stroke.[33] 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 events vs 0.2 events per 100 person-years, respectively; p = 0.01).[37] A recent analysis[40] of a large cohort study indicates that anticoagulation at INR ≥ 2.0 is associated with far better short-term survival should stroke occur. Stroke in patients with AF is generally more severe than stroke in patients without AF, probably reflecting a greater proportion of embolic events.[41] The available evidence indicates that full adjusted-dose oral VKA therapy (INR ≥ 2.0) effectively prevents such severe strokes in AF.

Oral anticoagulation vs other nonaspirin antiplatelet agents

In a randomized trial[42] 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 (MI), pulmonary embolism, or vascular death between the two groups (12% in the indobufen group vs 10% in the warfarin group; p = 0.47). 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 4, 5).

Standard vs low-dose anticoagulation

Several studies[22,30,36,43] 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 3). Very low intensity/low-dose anticoagulation proved unsuccessful. In a previous section, we included the SPAF III[22] and AFASAK 2[30] trials as tests of aspirin vs warfarin targeted at INR of 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,[22] which enrolled patients at high risk for stroke, was terminated early because of a substantially increased rate of primary outcome events in patients receiving combination therapy with fixed-dose, low-intensity warfarin (maximum daily dose of 3 mg targeting an INR of 1.2 to 1.5) plus aspirin, 325 mg/d. The event rate was 7.9%/yr among those randomly assigned to combination therapy vs 1.9%/yr among those randomized to adjusted-dose warfarin with a target INR of 2.0 to 3.0.[22] The absolute difference in stroke rate of 6%/yr translates into a NNT of 17. The high stroke rate in the combination therapy arm of this trial and the RRR 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 significant differences in the rates of major hemorrhage were detected between the two groups (Tables 4, 5).

In the section on the efficacy of aspirin vs warfarin, above, we reviewed the results of the AFASAK 2 study[30] 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. In essence, these statistically insignificant results were indeterminate.

PATAF,[36] AFASAK 2,[30] and the trial of Pengo et al[43] also compared low-dose warfarin vs adjusted-dose warfarin (INR, 2.0 to 3.0). In PATAF,[36] the risk of stroke was slightly lower in patients randomized to a target INR of 1.1 to 1.6 compared with oral anticoagulation with a target INR of 2.5 to 3.5 (risk reduction, 14%). In the latter two studies,[30,43] the risk of stroke was reduced by 13% and

42%, respectively, in the adjusted-dose anticoagulation groups (not statistically significant). Combining the results from all three trials in a meta-analysis[33] yielded an RRR of 38% (95% CI, − 20 to 68%) in favor of adjusted-dose oral anticoagulation, which was not statistically significant. Taken with the results of SPAF III,[22] however, it is clear that OAC therapy targeted at INR levels of ≤ 1.5 is ineffective.

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, such as those with prior stroke. This latter strategy has reduced embolic event rates in patients with mechanical heart valves.[44] 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.[17] We reported in the prior section on two trials, SPAF III[22] and AFASAK 2,[30] that combined very low intensities of anticoagulation with aspirin. The regimens used in these trials were insufficiently effective in preventing strokes (Tables 4, 5).

Two trials in AF used substantially higher intensities of anticoagulation combined with antiplatelet agents. The French Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontane (FFAACS) study[45] compared the oral anticoagulant fluindione (INR target 2.0 to 2.6) alone or combined with aspirin, 100 mg/d. Enrolled patients were at high risk of ischemic stroke using SPAF III criteria.[22] The trial was stopped early because of excessive hemorrhage in the group receiving combination therapy. At trial termination, only 157 patients had been entered, and mean follow-up was only 0.84 years.

In the much larger National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) study[46] (Tables 2–5), 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. The higher-risk patients were randomly assigned to treatment with OAC therapy using a target INR of 1.4 to 2.4 combined with the platelet cyclooxygenase inhibitor triflusal (600 mg/d, 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 INR of 2.0 to 3.0, or the combination of triflusal plus anticoagulation to INR of 1.25 to 2.0. Median follow-up was 2.6 years in the lower-risk group and 2.9 years in the higher-risk group. The primary outcome of the trial was a composite of thromboembolism plus cardiovascular death (from embolism, stroke, bleeding, sudden death, or heart failure, but not MI). The group receiving combination therapy had a significantly lower risk of primary outcome events 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 4, 5). 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[46] 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 nonthromboembolic events, 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.

Addition of aspirin to VKAs to reduce risk of coronary heart disease

Roughly one third of patients with AF also carry a diagnosis of coronary artery disease.[1] 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? At least one set of guidelines[17] has recommended such an approach. 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 groups 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.[47] Subsequent trials[48,49] 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. Patients in these coronary artery disease trials were, on average, approximately 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 meta-analysis[37] of AF trials comparing aspirin to OAC observed that OAC alone prevented coronary artery disease, as well as ischemic stroke, better than aspirin alone. From these data, one can infer that OAC alone targeted at INR of 2 to 3 can provide substantial protec-

tion against recurrent coronary disease. Addition of aspirin may provide some further protection against coronary disease but poses a small additional risk of hemorrhage. In patients with AF and atherosclerosis who are receiving OAC for stroke prevention, it is acceptable to add aspirin in doses up to 100 mg/d to OAC (INR, 2.0 to 3.0) for added prevention of ischemic coronary events, although this combination is associated with a higher risk of bleeding than treatment with either agent alone (further discussion of the use of antithrombotic agents in coronary artery disease can be found in the chapter by Harrington et al in this Supplement).

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 INR testing and dose adjustments. The quest for safer, more convenient alternatives has been particularly active and productive in recent years.

Because of its central role in thrombogenesis, thrombin (factor IIa) represents an attractive target for specific inhibition. Direct thrombin inhibitors bind to the active site of thrombin and prevent it from cleaving fibrinogen and factors V, VIII, XI, and XIII. Ximelagatran is an orally administered prodrug that is converted after absorption to the active direct thrombin inhibitor, melagatran. The compound has stable pharmacokinetics independent of the hepatic P_{450} enzyme system, and a low potential for food[50] or drug[51] interactions. Ximelagatran compared favorably with both low molecular weight heparin (LMWH) and adjusted-dose warfarin for prevention of venous thromboembolism,[52–55] and with warfarin for treatment of established deep vein thrombosis (DVT).[56]

Two large, long-term phase III studies compared ximelagatran with warfarin (INR 2 to 3) in patients with AF, Stroke Prevention using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Atrial Fibrillation (SPORTIF) III and SPORTIF V (Tables 2–5).[57] These trials included a combined patient population of 7,329 patients. In each trial, eligibility was based on current clinical indications for anticoagulation. Ximelagatran was administered in a fixed oral dose of 36 mg bid without routine coagulation monitoring or dose titration. SPORTIF III and V were designed to test whether ximelagatran was noninferior[58,59] to warfarin (INR, 2 to 3) within a prespecified absolute margin of 2.0%/yr for the difference in rates of primary events; that is, that the upper bound of the one-sided 97.5% CI for the difference in event rates would not exceed 2.0%/yr. The primary events were all stroke (ischemic or hemorrhagic) and systemic embolism. SPORTIF III[60] was an open-label study involving 3,407 patients randomized in 23 countries in Europe, Asia, and Australasia. SPORTIF V[61] followed exactly the same protocol in 3,922 patients randomized in North America, except that treatment was double blind. In both trials, the duration and pattern of AF were similar to cohorts of patients enrolled in previous trials of antithrombotic therapy. The mean age of randomized patients, who were predominantly white men, was 70 years. There was a history of stroke or TIA in approximately one fourth of the cohort, hypertension in over two thirds, and heart failure or left ventricular systolic dysfunction in over one third. Almost 75% of subjects had more than one risk factor for thromboembolism.

Among warfarin-assigned patients, INR values fell within the intended therapeutic range for 66% of the entire duration of exposure in SPORTIF III[60] and 68% in SPORTIF V,[61] and the mean INR was 2.5 across all measurements. After 4,941 patient-years of exposure in SPORTIF III,[60] a mean follow-up of 17 months per patient, 56 primary events occurred in the warfarin group, an annual rate of 2.3%, and 40 occurred in the ximelagatran group, 1.6%/yr (not significantly different). In SPORTIF V,[61] the mean duration of exposure was 20 months, during which there were 37 events in the warfarin group (1.2%/yr), and 51 events in the ximelagatran group (1.6%/yr).[61] The primary analysis of each trial supported the assertion of noninferiority and, when the results of both trials are taken together (according to a prespecified pooled analysis), the number of outcome events in patients assigned to either treatment was almost identical.

There was no significant difference between treatments in rates of hemorrhagic stroke, fatal bleeding, or other major bleeding. Major bleeding was defined as a decrease in hemoglobin of 2 g/dL or requiring transfusion, or involving a critical anatomic site. Elevations of serum transaminase enzymes above three times the upper limit of normal were observed in approximately 6% of patients in the ximelagatran group, typically between 2 months and 6 months after initiation of treatment, and these levels generally returned toward baseline either spontaneously or after cessation of treatment.

The results of SPORTIF III[60] and SPORTIF V[61] provide strong evidence that ximelagatran, 36 mg bid, is essentially equivalent to oral VKA therapy targeted at an INR of 2.0 3.0 in terms of stroke-preventive efficacy and risk of major bleeding. Since ximelagatran does not need anticoagulation monitoring or dose adjustment, it offers an attractive future treatment alternative to adjusted-dose warfarin. More information is needed on the risk of liver injury from ximelagatran. We will not include ximelagatran in our recommendations since it was not an approved therapy for AF when the panel wrote these guidelines.

Other molecular forms of synthetic oral direct antithrombin agents are in development. There are, as well, planned or ongoing trials involving long-acting subcutaneously administered heparinoids, the synthetic pentasaccharide factor Xa antagonist idraparinux, and combinations of platelet inhibitor agents such as aspirin and clopidogrel in patients with AF stratified on the basis of inherent thromboembolic risk. Molecules aimed at other targets are also under development for this indication, including those antagonizing the initial phase of tissue factor activation of factor VII and stimulation of fibrinolysis. Evaluation of each will require large trials because the active comparator (*eg*, warfarin) will necessarily be highly effective, resulting in low event rates.

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.[62–69] The trials enrolled only a small proportion of screened patients (*eg*, < 10% in SPAF[14]), relatively few very elderly patients (only 10% were > 80 years old[6]), and they used especially careful and frequent monitoring of anticoagulation intensity.

Studies of the outcomes of antithrombotic therapy in patients with AF in nontrial clinical settings have primarily 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 hemorrhagic outcome events leading to imprecise estimates of event rates.[62,63,65–69] Among survivors of ischemic stroke with AF, warfarin was more effective than aspirin for reducing recurrent stroke,[63] and recurrent stroke rates were lower during periods on vs off warfarin.[70] In two studies[65,66] of hospitalized patients with nonvalvular AF, the risk of stroke or TIA was lower in patients discharged receiving warfarin than in those receiving no antithrombotic therapy (adjusted relative risk [RR], 0.76[65]; and adjusted RR, 0.31,[66] respectively) and thromboembolic rates were lower with warfarin than aspirin. Among selected cohorts of patients with AF treated with anticoagulation, the risk of stroke varied from 1.3% annually[69] to 2.0 per 100 person-years.[64] In a large study[71] from Denmark involving 5,124 persons with AF based on hospital discharge or outpatient diagnoses between 1991 and 1998, investigators observed stroke rates of 3%/yr year overall, with a protective effect of warfarin in men (adjusted RR, 0.6; 95% CI, 0.4 to 1.0), but not in women. In these observational studies,[62–64,67] the 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.

In the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study,[72] a community-based cohort of 13,559 ambulatory adults with diagnosed nonvalvular AF was followed up for anticoagulation exposure and clinical outcomes. During follow-up of the entire cohort that included 598 validated thromboembolic events, the rate of thromboembolism was significantly lower on adjusted-dose warfarin compared to no warfarin therapy (including aspirin and no antithrombotic therapy): 1.36%/yr vs 2.53%/yr, respectively ($p < 0.001$), with a 49% (95% CI, 39 to 57%) adjusted risk reduction.[72] In the ATRIA study,[72] ICH rates were low on or off warfarin (0.51%/yr vs 0.33%/yr, respectively), although warfarin was associated with an increased risk of ICH (adjusted RR, 1.57; 95% CI, 1.10 to 2.26).[72] 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%/yr vs 0.23%/yr, respectively; $p = 0.003$) compared with no warfarin therapy.

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.

Risk stratification in patients with AF

Oral VKA therapy is very effective in decreasing the risk of ischemic stroke in patients with AF and considerably more effective than aspirin.[6,32,37] It is also clear that oral VKA therapy is associated with a higher frequency of hemorrhage and is more burdensome than aspirin. Each individual AF patient's risk of stroke and hemorrhage should be considered when making the decision about the optimal antithrombotic preventive therapy. Variation in guideline recommendations for antithrombotic therapy for AF primarily results from differences in risk stratification for ischemic stroke.[73,74] This section focuses on available literature informing risk stratification for stroke based primarily on randomized trials and large observational studies, while the chapter by Levine et al in this Supplement discusses issues surrounding 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[6,19,75–78] of antithrombotic therapy. The most commonly cited risk schema are derived from the pooled analyses from the Atrial Fibrillation Investigators (AFI)[6] and two analyses from the SPAF investigators (Table 7).[77,79]

The AFI group[6] 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). Of note, female gender, a history of congestive heart failure, and a history of coronary heart disease were not found to be significant predictors in multivariable analysis.

The SPAF investigators[79] conducted a pooled analysis of 854 patients assigned to aspirin from the first two SPAF trials. They identified three independent risk factors for stroke: the combination of female gender and age > 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 2,012 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

Table 7—*Comparison of Clinical Risk Factors for Stroke in AF in Randomized Trials of Antithrombotic Therapy

Characteristics	AFI[6]		SPAF I–II[79]†		SPAF I–III[77]‡	
	RR	Annual Risk, %	RR (95% CI)	Annual Risk, %	RR (95% CI)	Annual Risk, %
Age (per decade)	1.4	NA	3.7 (2.2–6.2)§	10.4	1.8	NA
Female gender	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	(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	6.7–8.2	NS	NA	NS	NA

*See Table 4 for expansion of abbreviation. NS = not statistically significant.
†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 aged ≥ 75 years.
‖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 of ≤ 25% by echocardiography.

treated with aspirin.[77] Five features significantly associated with an increased risk of stroke were age (RR, 1.8 per decade), female gender (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 along with 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 gender 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[22] 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).

Patients in the AFI analysis[6] with coronary disease had an elevated crude annual risk of stroke (*eg*, 8.2% for those with a history of MI). However, as noted above, in both the AFI and SPAF risk schemes, a history of coronary heart disease (*eg*, MI 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 hyperthyroidism, 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 ≥ 60 years of age, presumably reflecting an age-related reduction in the threshold for acquiring AF.[80] The prevalence of thyrotoxicosis in patients with AF is 2 to 5%.[80] Some studies[81–85] have reported a high frequency of stroke and systemic embolism in patients with thyrotoxic AF, although one study[86] did not find a statistically significant difference when patients with AF were compared to age- and sex-matched patients with normal sinus rhythm (NSR). Some of these studies have significant methodologic problems, which complicate interpretation of the results.[80] 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,[80] antithrombotic therapies should be chosen based on the presence of validated stroke risk factors (see Recommendations).

Comparison and validation of stroke risk stratification schemes

The AFI- and SPAF-based risk stratification schemes are largely consistent with each other. Prior stroke or TIA, older age, hypertension, and diabetes emerge from both analyses as risk factors for stroke in patients with AF. Unlike the AFI analysis,[6] the latest SPAF scheme found an adverse association with female gender and also 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 TIA, 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 at high risk for stroke, including those without any other risk factor for stroke. By contrast, the SPAF scheme would view women with AF ≤ 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 aged 65 to 75 years and men of any age without other risk factors applies to roughly 20% of the entire population with nonvalvular AF.[87]

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 had an increased annual risk of stroke (range, 4.3 to 8.1%), while low-risk patents 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 receiving aspirin). The features qualifying for these three risk strata are as follows: (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 (either of the following: history of hypertension and age $\leq$ 75 years, or diabetes); and (3) low risk: no high-risk or moderate-risk features. Among patients without a prior stroke or TIA (*ie*, primary prevention), high-risk patients overall faced a 7.1% (CI, 5.4 to 9.5%) annual risk of stroke, moderate-risk subjects had a 2.6% (CI, 1.9 to 3.6%) annual stroke risk, and low-risk subjects had a 0.9% (CI, 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.[77,78]

A modified stroke risk classification scheme, Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke (Doubled) [$CHADS_2$], integrates elements from the AFI and SPAF I-II schemes, and was tested among 1,733 hospitalized Medicare beneficiaries aged 65 to 95 years with nonvalvular AF who were not discharged receiving warfarin.[88] The $CHADS_2$ 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 $CHADS_2$ score in this elderly cohort, although few patients had a very high score of $\geq$ 5, and $<$ 7% had a score of zero (*ie*, low risk) [Table 8]. Modified 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 (95% CI, 4.2 to 6.5) for high-risk and 2.2 (95% CI, 1.1 to 3.5) for moderate-risk persons. The modified SPAF I-II scheme had high-risk (prior stroke or TIA, women $>$ 75 years, or recent congestive heart failure diagnosis), moderate-risk (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).

Table 8—*Risk of Stroke by $CHADS_2$ Score*

$CHADS_2$ Score[88]	Patients (n = 1,733)	Adjusted Stroke Rate (per 100 Person-Years),* (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)

*The adjusted stroke rate was the expected stroke rate per 100 person-years derived from the multivariable model assuming that aspirin was not taken. Adapted from Gage et al.[88]

A recent study[89] from the Framingham Heart Study examined risk factors for stroke among 705 patients with new-onset AF, after excluding patients who had an ischemic stroke, TIA, or death within 30 days of the AF diagnosis. The only significant multivariable predictors of ischemic stroke off oral VKAs were age (RR, 1.3 per decade), female gender (RR, 1.9), prior stroke or TIA (RR, 1.9), and diabetes (RR, 1.8), which are consistent with prior studies as described above. While systolic BP was not found to be an independent predictor of stroke off warfarin, it did reach statistical significance when warfarin was entered as a time-varying covariate in the Cox proportional hazards model. Using a scoring system that assigned points according to age, gender, systolic BP, and the presence of diabetes, prior stroke, or TIA, the proportion of patients with newly diagnosed AF considered at "low risk" varied from 14.3 to 30.6% if the threshold annual predicted rate of stroke ranged from $\leq$ 1.5 per 100 person-years to $\leq$ 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 $CHADS_2$ (10.2%) risk schemes. The actual observed annual stroke rates were relatively similar in these differently defined low-risk categories of patients (AFI, 0.9%; SPAF, 2.3%; $CHADS_2$, 1.7%).

Additional validation efforts have also been conducted comparing AFI, SPAF, and previous Sixth American College of Chest Physicians (ACCP) Consensus Conference[90] risk schemes. Among 259 elderly ($\geq$ 65 years old) participants with nonvalvular AF in the Cardiovascular Health Study,[91] annual rates of stroke using modified AFI/ACCP-6 criteria were 2.7% (95% CI, 1.7 to 4.1%) for high-risk subjects (prior stroke or TIA, hypertension, diabetes, congestive heart failure, or coronary heart disease) and 2.4% (95% CI, 0.9 to 5.1%) for moderate-risk subjects (age $\geq$ 65 years and no high risk features) subjects not receiving anticoagulation. Using the SPAF III criteria, annual stroke rates were relatively similar, ranging from 3.7% (95% CI, 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% (95% CI, 0.7 to 4.7%) for moderate risk (history of hypertension

and no high-risk features), and 1.7% (95% CI, 0.6 to 3.8%) for low risk (no moderate or high-risk features). Among 1,073 patients without prior stroke or TIA who participated in the SPAF III trial aspirin plus low-dose warfarin arm or SPAF III aspirin cohort study, the AFI, ACCP, and SPAF I-II criteria were evaluated.[92] The stroke rates for each risk stratum differed across the different risk schemes (Table 9), 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.

Echocardiographic predictors of stroke in AF

An AFI analysis[76] 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. While left atrial size and left ventricular systolic function can be adequately assessed by transthoracic 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[93,94] of outpatients with chronic AF. 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.[95,96] 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.[94] Of note, many of these abnormalities were observed in the descending aorta.[94] Additional TEE measures are currently being evaluated as potential stroke risk factors (*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.

Table 9—*Rate of Stroke by Risk Classification Scheme in SPAF III Test Cohort of Patients With AF Treated With Aspirin

	Stroke Risk Category, Rate per 100 Person-Years (95% CI)		
	High	Moderate	Low
AFI	2.9 (2.2–3.9)		0.3 (0.04–2.3)
SPAF I–II	7.2 (4.1–13.0)	3.2 (2.2–4.8)	1.1 (0.6–2.0)
ACCP	3.5 (2.6–4.7)	1.2 (0.5–2.8)	0.3 (0.05–2.5)

*Adapted from Pearce et al.[92] This analysis excludes patients with prior stroke or TIA.

Other potential risk factors for stroke in AF

Ongoing studies are also examining other types of characteristics that may refine current clinical and echocardiographic stroke risk stratification approaches, including genetic polymorphisms, abnormalities in hemostatic and thrombotic factors, platelet activation and aggregation pathways, and endothelial or vascular dysfunction.[91,97,98] At present, however, none have been identified that are sufficiently predictive for routine clinical use.

Pattern of AF and risk of stroke

While there remains a lack of consensus about how to best classify the pattern of AF,[17] a recurrent clinical concern is whether patients with PAF (intermittent AF), 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[80,99] suggested that PAF is associated with an intermediate risk of stroke between constant AF and NSR. However, when associated stroke risk factors are controlled for, clinical trial data suggest that PAF confers an RR of stroke similar to persistent or permanent AF.[6,100] 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 RRR provided by warfarin also appears similar for patients with PAF and persistent AF. This conclusion, however, is limited by the relatively small number of patients with PAF participating in the trials (approximately 12% of subjects in the first five randomized trials).[6] Analyses of PAF are further complicated by the fact that patients with PAF differ greatly in the frequency and duration of AF episodes 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[101–103] document a high prevalence of asymptomatic PAF, even among patients who are symptomatic with some episodes. 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.

Optimal intensity of anticoagulation for AF

There are only limited data directly comparing different intensities of oral anticoagulation in patients with AF.[22] 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 oral anticoagulation vs control employed a range of target intensities, both PTR based and INR based. The BAATAF[13] and SPINAF[15] studies used the lowest target intensity (PTR, 1.2 to 1.5), corresponding roughly to an INR range of 1.4 to 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,[22] even when combined with aspirin at 325 mg/d. There were too few patients in the AFASAK 2 study[30] to reliably determine the efficacy of low-dose warfarin (1.25 mg/d) or low-dose warfarin combined with aspirin (325 mg/d) compared with warfarin (INR, 2.0 to 3.0). 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[36] compared an INR range of 1.1 to 1.6 with a range of 2.5 to 3.5. No difference in efficacy was detected; however, the low event rates in this study limited the power to detect a difference. The EAFT study[18] found a decrease in efficacy below an INR of 2.0, but the trial could not assess finer gradations in INR < 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 the risk of ICH as a function of INR. Even in trials that enrolled the highest-risk patients, few thromboembolic events on anticoagulants were observed. In this circumstance, observational studies can be particularly informative because they can accumulate large numbers of outcome events. A case-control study[104] based in a large anticoagulation unit found that the risk of stroke increased at INR levels < 2.0. For example, 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[105] also found a sharp increase in risk of stroke among patients with AF and INR values < 2.0. INR levels > 2.0 do not appear to further lower the risk of ischemic stroke.[104,105] *Post hoc* analyses of the SPAF III trial[22] were consistent with these epidemiologic analyses.

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. In two studies,[26,27] the risk of ICH was fairly low at INR values < 4.0 but was sharply higher at greater INR levels. As noted above, the risk of ischemic stroke is low at INR values down to 2.0. A recent report from a large cohort study[40] indicates that INR levels < 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. 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 the very elderly (patients > 75 years old), who have higher risks than younger patients of both stroke and bleeding[24,26,106–108] on oral anticoagulants. One set of guidelines[17] suggested using a target INR of 1.6 to 2.5 for a subset of patients > 75 years old. This approach would expose many such patients to periods of relatively ineffective anticoagulation with minimal reduction in the absolute risk of ICH. Tight control near an INR level of 2.5 seems a preferable strategy based on existing evidence.[104]

The NASPEAF trial[46] 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. These provocative results should be confirmed before clinical recommendations can be made regarding such a strategy.

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,[109] while others at relatively low risk for stroke want to avoid the burdens and risks of VKAs and opt for aspirin.[109–111] 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 Italian Study on Complications of Oral Anticoagulant Therapy[107,112] and ATRIA[72] experiences demonstrate that low hemorrhage rates can be achieved in clinical practice outside of trials, particularly if well-organized anticoagulation clinics are involved.[6,23,72,112]

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 rather than avoiding a major hemorrhage as compared with physicians.[113] Many patients, in fact, assign utilities to a moderate-to-severe stroke that are equivalent to or worse than death.[111,114]

Decision analysis techniques have been used to evaluate the projected net benefit or harm associated with different antithrombotic treatment strategies in AF. 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*, warfarin use, 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.[115] The decision analysis approach has been modified in attempts to help individual patients make better choices about antithrombotic therapy in AF.[110] Strong evidence is currently lacking, however, that these decision support tools improve clinical outcomes.

Managing anticoagulant therapy for AF

General recommendations regarding management of oral anticoagulation are given in the chapter 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 2 weeks) risk of stroke in patients with AF is quite low since the annual risk even among high-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 surgery or related procedures (see 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 be > 2 weeks, a heparin/warfarin-bridging regimen should be considered.

Anticoagulation should be managed in a highly organized manner, preferably through specialized anticoagulation clinics. The 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 on "Antithrombotic and Thrombolytic Therapy for Ischemic Stroke."

Recommendations

1.1.1. In patients with persistent (also known as "sustained," and including patients categorized as "permanent" in certain classification schemes[17]) or paroxysmal (intermittent) AF at high risk of stroke (*ie*, having any of the following features: prior ischemic stroke, TIA, or systemic embolism, age > 75 years, moderately or severely impaired left ventricular systolic function and/or congestive heart failure, history of hypertension, or diabetes mellitus), we recommend anticoagulation with an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0) [**Grade 1A**].

1.1.2. In patients with persistent AF or PAF, age 65 to 75 years, in the absence of other risk factors, we recommend antithrombotic therapy (**Grade 1A**). Either an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0), or aspirin (325 mg/d) are acceptable alternatives in this group of patients who are at intermediate risk of stroke.

1.1.3. In patients with persistent AF or PAF < 65 years old and with no other risk factors, we recommend aspirin, 325 mg/d (**Grade 1B**).

Underlying values and preferences: Anticoagulation with an oral VKA, 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 1.1.2 and 1.1.3, 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 burden of managing anticoagulation.

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 AF risk of thromboembolism. 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 TEE study[116] among 19 patients with atrial flutter and 44 patients with AF 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[117,118] 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. A left atrial thrombus was found in 1 to 1.6%, a right atrial thrombus in 1% of subjects, and spontaneous left atrial echo contrast in 11 to 13%.[117,118] Thrombi in atrial flutter may be related to the duration of the arrhythmia. In a TEE study[119] 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. Finally, a 21% incidence of intra-atrial thrombi was described in 24 patients with atrial flutter undergoing TEE.[120] 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[121] of 100 patients suggests that the risk of stroke in patients with persistent atrial flutter may be higher than previously assumed. This conclusion is supported by the 7% risk of thromboembolism over 26 months of follow-up observed in a study[122] of 191 consecutive unselected patients referred for treatment of atrial flutter. 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 acquiring 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 suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (**Grade 2C**).

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[10] (see the chapters by Salem et al in this Supplement). Most of the randomized trials excluded such patients because anticoagulation was strongly believed to be beneficial. The NASPEAF trial[46] was notable in that it enrolled patients with mitral stenosis, but such patients were treated with one of two anticoagulation regimens (see above). 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[46] 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 chapter by Salem et al in this Supplement).

Recommendations

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

1.3.2. For patients with AF and prosthetic heart valves, we recommend anticoagulation with an oral VKA, such as warfarin **(Grade 1C+)**.

Remark: The target intensity of anticoagulation may be INR 3.0 (range, 2.5 to 3.5), *ie*, higher than the usual target INR of 2.5 (range, 2.0 to 3.0), and it may be appropriate to add aspirin, depending on type of prosthesis, its position, and other risk factors (see chapter by Salem et al in this Supplement).

1.4 AF following cardiac surgery

Atrial arrhythmias including AF occur in 20 to 50% of patients following open-heart surgery,[123,124] depending on definitions and methods of detection. After coronary artery bypass grafting (CABG), the incidence is 11 to 40%.[123,125,126] The incidence of postoperative AF is increasing, perhaps due more to the increasing age of surgical patients than to technical factors, and with this patient morbidity and hospital costs have increased as well. Atrial flutter is less common than AF following cardiac surgery.[127] 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 $>$ 90% of patients have resumed NSR by 6 to 8 weeks after surgery,[128] a rate of spontaneous resolution higher than for AF occurring in other situations.

A number of studies[129,130] have addressed clinical conditions that predict postoperative AF with conflicting results partly related to limited sample size. The most reproducible factor is older age. Other independent predictors include valvular heart disease, chronic lung disease, atrial enlargement, and preoperative atrial arrhythmias. Weber et al[130] developed a multivariate prediction scheme based on age, preoperative beta-blocker therapy, left ventricular ejection fraction, and P-wave duration on the ECG that identified patients with a 2.9-fold increased risk of AF with 62% sensitivity and 85% specificity. Pericarditis and increased sympathetic tone following cardiac surgery are among the factors that may trigger AF.

Patients who acquire AF following CABG surgery often demonstrate hemodynamic instability that requires inotropic support, intra-aortic balloon counterpulsation, or reoperation for bleeding.[126] The associated risk of thromboembolism, particularly ischemic stroke, occurs at a rate of 1 to 6%, and carries a high mortality rate (13 to 41%).[131–134] The risk of thromboembolism increases to almost 9% among CABG patients $\geq$ 75 years of age.[135–137] The economic impact of stroke after coronary revascularization is estimated to exceed $2 to $4 billion annually worldwide,[137] related to prolonged intensive care and total hospitalization days as well as long-term disability costs.[138,139]

It is important to consider prophylactic treatment of patients at greatest risk of acquiring postoperative AF through preoperative treatment with beta-blockers,[124,140] sotalol,[141–143] or amiodarone.[144,145] Nonpharmacologic measures such as biatrial overdrive pacing have also been used to reduce the incidence of postoperative AF in patients undergoing CABG surgery.[146]

When AF persists $>$ 48 h in the postoperative period following CABG surgery, anticoagulation with heparin or an oral VKA is appropriate,[147] 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 this maneuver reduces the incidence of postoperative thromboembolism, stroke, or the need for anticoagulation,[148–150] and several studies are in progress to evaluate this prospectively. Among other nonpharmacologic 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,[151] although this is currently performed more often in conjunction with mitral valve surgery.

Recommendation

1.4. For AF occurring shortly after open-heart surgery and lasting $>$ 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 several weeks fol-

lowing reversion to 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

Four decades have passed since synchronized capacitor discharge was first introduced by Lown and coworkers[152–154] 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), pharmacologic, 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[155] 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[153,156–159] also favor the use of adjusted-dose anticoagulation before cardioversion. Although sometimes occurring up to ≥ 10 days after cardioversion, most of these adverse events 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.[160] After conversion to NSR, atrial appendage dysfunction may persist or worsen, leading to a prothrombotic state, highlighting the importance of pericardioversion 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 to 4 weeks of prophylactic adjusted-dose warfarin before and after cardioversion.[161,162] 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 pharmacologic or spontaneous cardioversion of AF to NSR. Nonetheless, it seems prudent to administer anticoagulation in a similar manner for both pharmacologic and electrical conversion. Goldman[163] 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[153] reported in 450 electrical cardioversions. These rates are slightly higher than the incidence of clinical thromboembolism after a month of precardioversion warfarin (INR, 2.0 to 3.0) reported by the prospective and more contemporary Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE)[96] and the Ludwigshafen Observational Cardioversion studies[164] for patients undergoing DC cardioversion. In the ACUTE trial[96] of 603 patients randomly assigned to conventional therapy of 1 month of precardioversion anticoagulation with warfarin, 333 patients underwent DC cardioversion, with three subsequent neurologic events (0.9%). During the conventional treatment phase of the Ludwigshafen Observational study,[164] 357 subjects underwent DC cardioversion, with three neurologic events (0.8%) after successful cardioversion. Retrospective data from Europe[165] suggest there may be a particular benefit to a slightly higher INR immediately prior to cardioversion, with no embolic complications among 779 attempted cardioversions with an INR ≥ 2.5 vs a rate of 0.9% among 756 cardioversions if the INR was 1.5 to 2.4.

The mechanism of benefit conveyed by the month of warfarin prior to elective cardioversion had previously been ascribed to thrombus organization and adherence to the atrial wall.[163] More recently, serial TEE studies[166–168] among those presenting with new onset AF and atrial thrombi on initial TEE have demonstrated resolution of the thrombi after 1 month of warfarin in the majority of subjects. However, it is likely that thrombi persist in a significant minority.[164] It thus appears that the month of warfarin may facilitate both "silent" thrombus resolution and thrombus organization/adherence.

The immediate postcardioversion 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.[169–172] These data underscore the importance of therapeutic anticoagulation during the pericardioversion 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.[173–175] Anecdotally, a "fibrillatory" pattern has been found in the appendage with sinus-type activity on the surface ECG and transmitral Doppler spectra.[176] The duration of atrial recovery appears to be directly related to the duration of AF prior to cardioversion.[177,178] For these reasons, adjusted-dose anticoagulation should be continued for 1 month 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.

Conventional vs TEE-guided cardioversion

Over the past 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.[95,166,167,172,175] While the detection of left atrial appendage thrombi is unreliable utilizing conventional transthoracic echocardiography, biplane and multiplane TEE have demonstrated very high accuracy,[11,179] and therefore offer the opportunity to perform early cardioversion for those in whom no atrial

appendage thrombi are observed. 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 pericardioversion or postcardioversion periods. Data from several studies[95,96,166,167,172,175] currently suggest rates of thromboembolism that are similar 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.[180] Limitations of the TEE approach include patient discomfort, rare procedural complications, and limited availability at some centers.

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 pericardioversion period through a full month after cardioversion.[181–184] 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[96] enrolled 1,222 patients with AF for whom elective electrical cardioversion was planned in order to compare the conventional vs the potentially expedited TEE approach; 619 subjects were randomly assigned to the TEE arm. There were five embolic events in the TEE arm vs three events in the conventional arm (p value not significant). It is worth noting that among those assigned to the TEE arm, only 549 patients actually underwent TEE, including 425 patients who subsequently underwent DC cardioversion. Among these 425 patients, four 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). Among the 603 patients in the conventional anticoagulation regimen arm, only 333 patients 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 following randomization. In contrast, other nonrandomized prospective studies have 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.[185]

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[199] reported a 13% prevalence of atrial thrombi on TEE among patients with AF of < 72 h duration. Subsequently, data were reported from a study[186] of 357 patients who had a symptomatic duration of AF for < 48 h; 250 patients converted spontaneously and 107 patients underwent pharmacologic or electrical cardioversion, all without screening TEE or a month 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 and colleagues[165] reported on retrospective data regarding 258 patients with AF < 2 days undergoing cardioversion. One embolic event (0.5%) occurred in 198 patients who did not receive preconversion or postcardioversion warfarin, with no events (0%) among 60 patients who did receive preconversion and postcardioversion warfarin. Though low stroke risk was seen 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 partial thromboplastin time [PTT] of 60 s (range, 50 to 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 pericardioversion period. There are no randomized trials comparing these approaches in patients with AF of < 48 h in duration.

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. 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.

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 thromboem-

bolic events in a total of 207 patients from two series[157,187] who underwent elective cardioversion for atrial flutter without anticoagulation prior to or after cardioversion. More recent retrospective data suggest a significant risk of thromboembolism. Gallagher et al[165] retrospectively reviewed data from 222 patients with atrial flutter/atrial tachycardia undergoing cardioversion without warfarin, with two confirmed and an additional two probable thromboembolic events. Five events occurred among 292 patients who received warfarin before and after 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[121,122,188] have shown no events among patients receiving precardioversion and postcardioversion warfarin therapy.

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.[116,119,189,190] These changes predispose to *de novo* thrombus formation, which has been documented in patients with atrial flutter.[191] 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.[189,192]

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 1 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 recently completed randomized trials, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)[193] and the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation Study (RACE)[194] 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 long-term 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 rate AF is 40 to 60% at 1 year.[195,196] Many episodes of recurrent AF are not symptomatic and may be undiagnosed if paroxysmal.[102] During these asymptomatic periods of AF, thrombi may form which can cause clinical thromboembolism. (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.[76,94]

Rate control does not require long-term 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 atrioventricular node and pacemaker insertion.

Three randomized trials[193,194,197] have compared rhythm-control 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. The largest trial, AFFIRM,[193] included 4,060 patients with recurrent AF. 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[194] enrolled 522 patients with recurrent AF or atrial flutter < 1 year in duration who underwent cardioversion on one or two occasions within the prior 2 years. 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 Pharmacologic Intervention in Atrial Fibrillation trial,[197] 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-control and rhythm-control approaches are acceptable. However, the larger and longer AFFIRM[193] and RACE[194] 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 high risk for stroke should receive long-term anticoagulation with an oral VKA such as warfarin to a target INR of 2.5 (range, 2.0 to 3). Further analyses of data from the AFFIRM study[193] and other studies 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 (target INR, 2.5; range, 2.0 to 3.0), for 3 weeks before elective cardioversion and for at least 4 weeks after successful cardioversion (**Grade 1C+**).

Remark: This recommendation applies regardless of a patient's risk factor status. Continuation of anticoagulation beyond 4 weeks is based on whether the patient has experienced more than one episode of AF and on their risk factor status. Patients experiencing more than one episode of AF should be considered as having PAF (see Recommendations 1.1.1, 1.1.2, and 1.1.3).

2.1.2. For patients with AF of $\geq$ 48 h or of unknown duration undergoing pharmacologic or electrical cardioversion, an alternative to the strategy outlined in Recommendation 2.1.1 is anticoagulation (immediate unfractionated IV heparin with target PTT of 60 s [range, 50 to 70 s], or at least 5 days of warfarin with target INR of 2.5 [range, 2.0 to 3.0] at the time of cardioversion) and a screening multiplane TEE be performed. If no thrombus is seen and cardioversion is successful, 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**).

Remark: The utility of the conventional and TEE-guided approaches is likely comparable. These recommendations apply regardless of a patient's risk factor status. Continuation of anticoagulation beyond 4 weeks is based on whether the patient has experienced more than one episode of AF and on their risk factor status. Patients experiencing more than one episode of AF should be considered as having PAF (see Recommendations 1.1.1, 1.1.2, and 1.1.3).

2.1.3. For patients with AF of known duration $<$ 48 h, we suggest that cardioversion be performed without 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 their risk factor status. Patients experiencing more than one episode of AF should be considered as having PAF (see Recommendations 1.1.1, 1.1.2, and 1.1.3).

2.1.4. For emergency cardioversion where a TEE-guided approach is not possible, we suggest IV unfractionated heparin (target PTT, 60 s; range, 50 to 70 s) be started as soon as possible, followed by 4 weeks of anticoagulation with an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0) if NSR persists after cardioversion (**Grade 2C**).

Remark: Continuation of anticoagulation beyond 4 weeks is based on whether the patient has experienced more than one episode of AF and on their risk factor status. Patients experiencing more than one episode of AF should be considered as having PAF (see Recommendations 1.1.1, 1.1.2, and 1.1.3).

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**).

Summary of Recommendations

1.0 Long-term Antithrombotic Therapy for Chronic Atrial Fibrillation or Atrial Flutter, Anticoagulants and Antiplatelet Agents

1.1 Atrial fibrillation

1.1.1. In patients with persistent (also known as "sustained," and including patients categorized as "permanent" in certain classification schemes[17]) or paroxysmal (intermittent) AF at high risk of stroke (*ie*, having any of the following features: prior ischemic stroke, TIA, or

systemic embolism, age > 75 years, moderately or severely impaired left ventricular systolic function and/or congestive heart failure, history of hypertension, or diabetes mellitus), we recommend anticoagulation with an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0) [**Grade 1A**].

1.1.2. In patients with persistent AF or PAF, age 65 to 75 years, in the absence of other risk factors, we recommend antithrombotic therapy **(Grade 1A)**. Either an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0), or aspirin, 325/d, are acceptable alternatives in this group of patients who are at intermediate risk of stroke.

1.1.3. In patients with persistent AF or PAF < 65 years old and with no other risk factors, we recommend aspirin, 325 mg/d (**Grade 1B**).

Underlying values and preferences: Anticoagulation with an oral VKA, 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 1.1.2 and 1.1.3, 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 burden of managing anticoagulation.

1.2 Atrial flutter

1.2. For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (**Grade 2C**).

1.3 Valvular heart disease and atrial flutter

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

1.3.2. For patients with AF and prosthetic heart valves, we recommend anticoagulation with an oral VKA, such as warfarin (**Grade 1C+**).

Remark: The target intensity of anticoagulation may be INR 3.0 (range, 2.5 to 3.5), *ie*, higher than the usual target INR of 2.5 (range, 2.0 to 3.0), and it may be appropriate to add aspirin, depending on type of prosthesis, its position, and other risk factors (see chapter by Salem et al in this Supplement).

1.4 Atrial fibrillation following cardiac surgery

1.4. For AF occurring shortly after open-heart surgery and lasting > 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 several weeks following reversion to NSR, particularly if patients have risk factors for thromboembolism (**Grade 2C**).

2.0 Anticoagulation for Elective Cardioversion of Atrial Fibrillation or Atrial Flutter Patients

2.1.1. 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 (target INR, 2.5; range, 2.0 to 3.0), for 3 weeks before elective cardioversion and for at least 4 weeks after successful cardioversion (**Grade 1C+**).

Remark: This recommendation applies regardless of a patient's risk factor status. Continuation of anticoagulation beyond 4 weeks is based on whether the patient has experienced more than one episode of AF and on their risk factor status. Patients experiencing more than one episode of AF should be considered as having PAF (see Recommendations 1.1.1, 1.1.2, and 1.1.3).

2.1.2. For patients with AF of ≥ 48 h or of unknown duration undergoing pharmacologic or electrical cardioversion, an alternative to the strategy outlined in Recommendation 2.1.1 is anticoagulation (immediate unfractionated IV heparin with target PTT of 60 s [range, 50 to 70 s], or at least 5 days of warfarin with target INR of 2.5 [range, 2.0 to 3.0] at the time of cardioversion) and a screening multiplane TEE be performed. If no thrombus is seen and cardioversion is successful, 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**).

Remark: The utility of the conventional and TEE-guided approaches is likely comparable. These recommendations apply regardless of a patient's risk factor status. Continuation of anticoagulation beyond 4 weeks is based on whether the patient has experienced more than one episode of AF and on their risk factor status. Patients experiencing more than one episode of AF should be considered as having PAF (see Recommendations 1.1.1, 1.1.2, and 1.1.3).

2.1.3. For patients with AF of known duration < 48 h, we suggest that cardioversion be performed without 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 their risk factor status. Patients experiencing more than one episode of AF should be considered as having PAF (see Recommendations 1.1.1, 1.1.2, and 1.1.3).

2.1.4. For emergency cardioversion where a TEE-guided approach is not possible, we suggest IV unfractionated heparin (target PTT, 60 s; range, 50 to 70 s) be started

as soon as possible, followed by 4 weeks of anticoagulation with an oral VKA, such as warfarin (target INR, 2.5; range, 2.0 to 3.0) if NSR persists after cardioversion (**Grade 2C**).

Remark: Continuation of anticoagulation beyond 4 weeks is based on whether the patient has experienced more than one episode of AF and on their risk factor status. Patients experiencing more than one episode of AF should be considered as having PAF (see Recommendations 1.1.1, 1.1.2, and 1.1.3).

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**).

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