Antithrombotic Therapy in Atrial Fibrillation

Gregory W. Albers, MD, Chair; James E. Dalen, MD, MPH; Andreas Laupacis, MD; Warren J. Manning, MD; Palle Petersen, MD, DMSc; and Daniel E. Singer, MD

Abbreviations: ACUTE = Assessment of Cardioversion Using Transesophageal Echocardiography; AF = atrial fibrillation; AFASAK = Atrial Fibrillation Aspirin and Anticoagulation; AFPI = Atrial Fibrillation Investigators; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAF = Canadian Atrial Fibrillation Anticoagulation; CI = confidence interval; DC = direct current; EAF = European Atrial Fibrillation Trial; ESPS = European Stroke Prevention Study; INR = international normalized ratio; LV = left ventricular; MI = myocardial infarction; NNT = number needed to treat for 1 year; OAC = oral anticoagulation; PAF = paroxysmal atrial fibrillation; RR = risk reduction; RRR = relative risk reduction; SIFA = Stroke Prevention in Nonrheumatic Atrial Fibrillation; TIA = transient ischemic attack

Atrial fibrillation (AF) is the most common sustained arrhythmia and is an important independent risk factor for stroke. AF is present in > 2 million people in the United States. Its prevalence begins to increase in both genders after age 40 years and rises rapidly after age 65 years. AF is particularly common in the elderly, reaching a prevalence of roughly 10% in those > 80 years old. The median age of patients with AF is approximately 75 years. The condition is more prevalent in men than in women. However, because there are more women than men in the older age groups, the absolute number of women and men with AF is similar.

The rate of ischemic stroke among patients with AF included in clinical trials of primary prevention and not treated with antithrombotic therapy averages about 5%/yr, with wide, clinically important variation among subpopulations of AF patients. AF becomes an increasingly important cause of stroke with advancing age. In the Framingham Heart Study, the attributable risk of stroke in AF patients rose from 1.5% in the 50- to 59-year age group to 23.5% in the 80- to 89-year age group. In patients > 80 years old, AF was the only cardiovascular condition associated with an increased risk of stroke.

This chapter deals primarily with stroke prevention when AF is not associated with rheumatic mitral valve disease or prosthetic heart valves. These specific conditions are discussed in the chapters on valvular heart disease and prosthetic heart valves.

1. Efficacy of Long-term Antithrombotic Therapy in AF

Study Design

During the last decade, many studies assessing the efficacy and safety of different antithrombotic therapies for the prevention of stroke in AF have been published (Tables 1–4). The study designs will be briefly described, according to the type of antithrombotic regimen studied.

Oral Anticoagulation vs Control: Six studies were randomized, controlled trials comparing oral anticoagulation (OAC) with control. In the Canadian Atrial Fibrillation Anticoagulation (CAF) study and the Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) study, assignment to anticoagulation or placebo groups was double blind, while anticoagulation administration was open labeled in the Stroke Prevention in Atrial Fibrillation (SPAF)-1 study. The Atrial Fibrillation Aspirin and Anticoagulation (AFASAK)-1 study, and the European Atrial Fibrillation Trial (EAFT). In the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF), the control group was not administered anticoagulation but could choose to take aspirin (46% of the patient-years in the control group were contributed by patients who were receiving aspirin regularly). Among the studies, the target international normalized ratio (INR) varied from approximately 1.4 to 2.8 in the SPINAF study to 2.5 to 4.0 in the EAFT.

Aspirin vs Placebo or Control: Five studies compared aspirin with control: four studies were placebo-controlled, and one study had a noninterventional control. The dose of aspirin varied between 325 mg/d and 125 mg every second day.

OAC vs Aspirin: Five studies compared OAC with aspirin. In SPAF-2, patients who had been randomized to aspirin or warfarin in the SPAF-1 study continued with their assigned treatment. Patients originally assigned to placebo and 419 new patients were randomized to warfarin or aspirin. Randomization was stratified according to the patient’s age (< 75 years; ≥ 75 years).

OAC vs Low-Dose OAC and Aspirin: In the SPAF-3 high-risk study, AF patients who had at least one of four thromboembolic risk factors (congestive heart failure or left ventricular [LV] fractional shortening ≤ 25%, history of a previous thromboembolism, systolic BP > 160 mm Hg at study entry, or female gender > 75 years old) were randomized 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 to adjusted-dose warfarin (target INR 2.0 to 3.0). The AFASAK-2 study randomized patients to warfarin, 1.25 mg/d, and aspirin, 300 mg/d, or to adjusted-dose warfarin (target INR 2.0 to 3.0).

OAC vs Low-Dose Anticoagulation: Three studies have compared adjusted-dose anticoagulation with lower doses of OAC: warfarin, 1.25 mg/d, in two studies, and warfarin (target INR 1.1 to 1.6) in the third study.

Other Antiplatelet Agents: The Studio Italiano Fibrillazione Atriale (SIFA) study randomized AF patients with a recent nondisabling stroke or transient ischemic attack (TIA) to therapy for 1 year with either indobufen...
(a reversible inhibitor of cyclooxygenase), 200 mg bid, or warfarin (INR 2.0 to 3.5) within 15 days of the qualifying ischemic event. In the second European Stroke Prevention Study (ESPS-2), patients with a TIA or stroke within the previous 3 months were randomized to one of four treatments: (1) placebo; (2) aspirin, 25 mg/d bid; (3) extended-release dipyridamole, 200 mg/d bid; or (4) aspirin, 25 mg/d bid, and extended-release dipyridamole, 200 mg/d bid.

**Aspirin Therapy in Low-Risk Patients:** Finally, in the SPAF-3 low-risk study, AF patients considered to be at low risk of stroke, based on the absence of any of the four risk factors in the SPAF-3 high-risk study (see above), were administered aspirin only, 325 mg/d, and followed in a nonrandomized, longitudinal, cohort study. This nonrandomized study does not provide data regarding the efficacy of aspirin for stroke prevention, but it is useful in determining the risk of stroke in selected patients with AF who are treated with aspirin.

**Outcome Events**

The primary outcome events in each study are listed in Table 1. The data reported herein are the results of the intention-to-treat analyses, although it is not clear if the

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<thead>
<tr>
<th>Studies</th>
<th>Patients, No.</th>
<th>Treatment Arms, No.</th>
<th>Mean Follow-up Duration, yr</th>
<th>Primary Outcome Measure</th>
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<td>1.2</td>
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<td>Pengo et al</td>
<td>303</td>
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<td>729</td>
<td>3</td>
<td>2.7</td>
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* = Ischemic stroke; NSE = Non-CNS systemic embolus; ICB = Intracranial bleed; FB = fatal bleed; VD = vascular death; PE = pulmonary embolism; NA = not available.
† This represents only the patients in ESPS-2 with AF.
‡ Primary outcome not specified; however, sample size calculated using ischemic stroke and intracranial bleed.

(a reversible inhibitor of cyclooxygenase), 200 mg bid, or warfarin (INR 2.0 to 3.5) within 15 days of the qualifying ischemic event. In the second European Stroke Prevention Study (ESPS-2), patients with a TIA or stroke within the previous 3 months were randomized to one of four treatments: (1) placebo; (2) aspirin, 25 mg/d bid; (3) extended-release dipyridamole, 200 mg/d bid; or (4) aspirin, 25 mg/d bid, and extended-release dipyridamole, 200 mg/d bid.

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<td>AFASAK-1</td>
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<td>Low risk</td>
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<th>Table 2—Treatment Arms in AF Studies</th>
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<td>Hellemons et al</td>
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* = ESPS-2 also included two other treatment groups: (1) extended-release dipyridamole, 200 mg bid; (2) aspirin, 25 mg bid, plus extended-release dipyridamole, 200 mg bid.
† Indobufen, 200 mg bid (not aspirin).
‡ Prothrombin time ratio-based target range; INR range is estimated.
§ Posada and Barriales evaluated two doses of aspirin: 125 mg qd and 125 mg every other day.
data in the study by Posada and Barriales23 were analyzed according to the intent-to-treat principle. All studies considered stroke a primary event, and some studies 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 transfusion was required, if the patient was hospitalized, or if the bleeding occurred in a critical anatomic location (eg, intracranial, perispinal). The criteria used by the BAATAF investigators17 were different: intracranial bleeding, fatal bleeding, or bleeding leading to transfusion of \( \geq 4 \) U of blood within 48 h.

**Primary Results**

The primary results of the studies are summarized in Tables 3, 4.

**OAC vs Control:** In all randomized studies comparing adjusted-dose warfarin anticoagulation with placebo or control, there was a decrease in the rate of primary outcome events in adjusted-dose anticoagulation-treated patients compared with control patients, which reached or exceeded conventional statistical significance in all studies except the CAFA study.18 The CAFA study18 was stopped early because of the results of the other trials (Table 3).

Pooled the results of all of these trials except the EAFT7 in an intention-to-treat analysis revealed an annual stroke rate of 4.5% for the control patients and 1.4% for the adjusted-dose warfarin patients (relative risk reduction [RRR] = 68%; 95% confidence interval [CI], 50 to 79%; number needed to treat for 1 year [NNT] = 32).6 The percentage of strokes that were classified as moderate, severe, or fatal ranged between 43% and 64%. Anticoagulation was effective for preventing strokes of all severities; there was no evidence that the strokes occurring in anticoagulated patients were more severe. In the EAFT,7 which enrolled only patients with a TIA or stroke within the previous 3 months, the RRR was virtually identical, although the absolute risk of stroke was higher; the

<table>
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<th>Table 3—Primary Outcome Events in AF Studies*</th>
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<td><strong>Studies</strong></td>
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<tr>
<td>OAC vs control</td>
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<td>AFASAK-1†</td>
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<td>BAATAF†</td>
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<td>CAFA†</td>
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<td>EAFT‡</td>
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<td>Aspirin vs control</td>
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<td>EAFT‡</td>
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<td>OAC vs aspirin</td>
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<td>EAFT‡</td>
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<td>OAC vs low-dose OAC plus aspirin</td>
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<tr>
<td>OAC vs indobufen</td>
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<td>SIFA10</td>
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*NS = not significant.
†Based on intention-to-treat analysis.
‡ESPS-2 also had two other treatment arms: dipyridamole, 200 mg bid (annual stroke rate, 15.1%), and dipyridamole, 200 mg bid and aspirin 25 mg bid (annual stroke rate, 11.0%).

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annual rate of stroke in control patients was 12% vs 4% in anticoagulated patients (RRR = 66%; 95% CI, 43 to 80%; \( p < 0.001; \text{NNT} = 13 \)).

There was no significant increase in major bleeding events in adjusted-dose anticoagulation-treated patients in these randomized trials (Table 4). In five of the studies (the EAFT\(^7\) was excluded), anticoagulation lowered the death 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%).\(^6\)

**Aspirin vs Placebo or Control:** The evidence supporting the superiority of aspirin to placebo is less robust than the evidence for warfarin. In the AFASAK-1 study,\(^15\) the EAFT,\(^7\) the ESPS-2,\(^11,12\) and the study by Posada and Barriales,\(^23\) the relative reduction in the stroke rate was generally small and not statistically significant. In contrast, the SPAF-1\(^6\) showed a statistically significant RRR of 42%. In the SPAF-1,\(^16\) the efficacy of aspirin was apparent in only one of the two component subtrials. When the data from the AFASAK-1 study,\(^15\) the EAFT,\(^7\) and the SPAF-1\(^6\) were combined in an individual-patient analysis, aspirin therapy was associated with a 21% reduction in the risk of ischemic stroke (annual stroke rate, 8.1% in control patients and 6.3% in aspirin-treated patients; \( p = 0.05; 95\% \text{ CI}, 0 \text{ to } 38\% \)).\(^26\) One meta-analysis\(^27\) combining all four published trials as well as a small unpublished study found a virtually identical 22% reduction in the risk of stroke. A second meta-analysis\(^28\) concluded the aspirin results were heterogeneous, resulting in a substantially broader CI: RRR = 24% (range, −33% to +66%).

**Adjusted-Dose Anticoagulation vs Aspirin:** In the AFASAK-1 study\(^15\) and the EAFT,\(^7\) adjusted-dose OAC
decreased the risk of primary events by 48% and 40%, respectively, compared with aspirin, 300 mg/d (both results were statistically significant). The results of the SPAF-2 study24 were reported separately for patients \( \leq 75 \) years of age (mean age, 65 years) and for patients \( > 75 \) years (mean age, 80 years; Table 3). In the younger group, adjusted-dose warfarin therapy decreased the rate of stroke by 33%, compared with a 27% reduction in the older patients (both differences were not statistically significant). However, in SPAF-2,22 many of the strokes occurred in individuals who had discontinued treatment with OACs. The AFASAK-2 study13 was stopped about midway through the planned enrollment; therefore, it did not have substantial power to detect a difference between the two drugs. In the AFASAK-2 study,13 the annual risk of primary events was increased slightly in adjusted-dose warfarin-treated patients compared with those receiving aspirin (3.4% vs 2.7%), although the difference was not statistically significant. The study by Hellemons et al25 reported a 19% RRR of stroke with OAC, which was not statistically significant. Finally, the SPAF-3 high-risk study8 found a marked superiority of adjusted-dose warfarin (INR 2.0 to 3.0) over low-dose warfarin plus aspirin (see next paragraph). Over all, these results suggest that the RRR associated with adjusted-dose warfarin is considerably greater than that provided by aspirin. A recent meta-analysis27 of these five studies reported a 36% RRR (95% CI, 14 to 52%) of all stroke with adjusted-dose OAC compared with aspirin, and a 46% reduction (95% CI, 27 to 60%) in the risk of ischemic stroke. The difference between the two analyses was largely due to the increased rate of intracranial hemorrhage in the SPAF-2 study.22 Of note, the target INR range (2.0 to 4.5) in the SPAF-2 study28 extended above currently recommended intensities.

**Adjusted-Dose Anticoagulation vs Low-Dose Anticoagulation Plus Aspirin:** The SPAF-3 high-risk study8 was terminated early at the suggestion of the External Safety Monitoring Committee because of a substantially increased rate of primary outcome events in patients receiving combination therapy with fixed-dose, low-intensity warfarin (INR 1.2 to 1.5; maximum daily dose, 3 mg) plus aspirin, 325 mg/d (7.9%/yr) compared with those receiving adjusted-dose warfarin with a target INR of 2.0 to 3.0 (1.9%/yr). 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 trial8 suggests that the low-intensity anticoagulation selected for this study was ineffective in these high-risk AF patients. In addition, no evidence of a 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 (Table 4). The smaller AFASAK-2 study13 of moderate-risk patients (excluded were patients <60 years old with lone AF and those with a history of stroke or TIA in the past 6 months or BPs \( > 180/100 \) mm Hg) was stopped prematurely following the publication of the SPAF-3 data.8 Analysis of their data demonstrated no differences, with an annual rate of primary events of 3.4% in patients receiving adjusted-dose warfarin (INR 2.0 to 3.0) compared with 3.2% in patients receiving aspirin, 300 mg, with fixed-dose warfarin, 1.25 mg/d.13

**Adjusted-Dose OAC vs Low-Dose Anticoagulation:** In the studies13,24 comparing adjusted-dose warfarin with warfarin, 1.25 mg/d, the risk of stroke was reduced by 13% and 42% in the adjusted-dose anticoagulation groups, respectively, both not statistically significant. In another recent study,25 the risk of stroke was slightly lower in patients randomized to a target INR of 1.1 to 1.6, compared with OAC with a target INR of 2.5 to 3.5 (RRR = 14%), although this difference is likely due to chance. Combining the results from all three trials in a meta-analysis27 yielded an RRR of 38% (95% CI, 20 to 68%) in favor of adjusted-dose OAC, which was not statistically significant.

**OAC vs Other Antiplatelet Agents:** In the one randomized trial10 comparing adjusted-dose warfarin with indobufen, there was no significant difference in the incidence of primary events (stroke, myocardial infarction [MI], pulmonary embolism, or vascular death) between the two groups (12% in indobufen group vs 10% in warfarin group; \( \rho = 0.47 \)). There were four major GI hemorrhages in the warfarin group compared with none in the indobufen group. The frequency of major bleeding episodes was 0.9% in the warfarin group and 0% in the indobufen group. Indobufen is not currently available in North America. However, the SIFA study10 results suggest that additional studies of this agent may be warranted.

For a discussion of when to begin anticoagulation after a stroke in AF patients, please refer to the chapter on “Antithrombotic and Thrombolytic Therapy for Ischemic Stroke.”

**Risk of Intracranial Hemorrhage**

Intracranial hemorrhage is the most feared complication of anticoagulant therapy because it is frequently fatal or permanently disabling. Observational studies29,30 from large anticoagulation clinics demonstrate that the risk of intracranial hemorrhage rises dramatically at INR values >4.0 to 5.0. Overall, the initial randomized trials comparing anticoagulation with control or placebo for AF were reassuring about the rate of intracranial hemorrhage (Table 4). However, a substantially higher rate of intracranial hemorrhage was observed in the SPAF-2 study.22 In particular, seven intracranial hemorrhages were observed among patients >75 years old, for an annualized rate of 1.8%, compared with 0.8% in patients receiving aspirin. In contrast, taken together, the earlier primary prevention trials observed a rate of intracranial hemorrhage of only 0.3%/yr among patients >75 years old, one sixth of that seen in the SPAF-2 study.31 In the secondary prevention EAFT study,7,32 the average age at entry was 71 years and no intracranial hemorrhages were reported, although a CT scan was not done in all patients with symptoms of stroke. In the high-risk arm of SPAF-39 (mean age, 71 years; mean INR, 2.4; target INR, 2.0 to 3.0), the rate of intracranial hemorrhage was 0.5%/yr compared to a rate of 0.9%/yr in the aspirin plus low-dose warfarin arm. The
AFASAK-2 study\textsuperscript{14} recently reported two intracranial hemorrhages in the INR 2.0 to 3.0 arm for an annual rate of 0.6%, compared to 0 to 0.5%/yr rates in the three other treatment arms.

The reasons for the unusually high intracranial hemorrhage rate in the SPAF-2 trial\textsuperscript{25} in patients > 75 years old as compared with the other studies are not entirely clear, although the patients were older than in any other AF trial, and the target anticoagulation intensity was high (INR 2.0 to 4.5). The importance of high INR levels in increasing the risk of intracranial hemorrhage was further reinforced by the SPIRIT trial,\textsuperscript{34} a non-AF secondary stroke prevention trial that used an INR target intensity of 3.0 to 4.5. In the SPIRIT trial,\textsuperscript{34} the annual rate of intracranial hemorrhage was > 3% among patients treated with anticoagulants. This rate was strongly related to INR values, particularly INR > 4.0.

**Optimal Level of Anticoagulation for AF**

Only limited data are available directly comparing different intensities of OAC in patients with AF.\textsuperscript{8} However, the results of the randomized trials and of observational studies of clinical practice provide fairly consistent evidence about the optimal level of anticoagulation for AF. The initial set of randomized trials of OAC vs control employed a range of target intensities, both prothrombin time ratio-based and INR-based. The BAATAF study\textsuperscript{17} and the SPINAF study\textsuperscript{19} used the lowest target intensity, prothrombin time ratio 1.2 to 1.5, corresponding roughly to an INR range of 1.5 to 2.7. Anticoagulation appeared just as effective at preventing strokes in these trials as in the others using a higher target intensity. A target INR of 1.2 to 1.5 was ineffective in the high-risk SPAF-3 trial,\textsuperscript{8} even when combined with aspirin, 325 mg/d. There were too few patients in the AFASAK-2 study\textsuperscript{14} 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; annual event rates of 3.9%, 3.2%, and 3.4%, respectively). To our knowledge, no trials have compared target intensities between an INR of 1.5 to 2.0 with an INR between 2.0 and 3.0 in a randomized fashion. One trial\textsuperscript{35} compared an INR range of 1.1 to 1.6 with an INR range of 2.5 to 3.5. No difference in efficacy was detected; however, the low event rates in this study limit the power to detect a difference. The EAFT\textsuperscript{32} found a decrease in efficacy below an INR of 2.0, but the trial could not assess gradations in INR < 2.0. A case-control study\textsuperscript{35} based in a large anticoagulation unit found that INR levels > 2.0 added little efficacy, while 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\textsuperscript{36} also found a sharp increase in risk of stroke among AF patients with INR values < 2.0.

The optimal level of anticoagulation in AF is that level that preserves efficacy in preventing ischemic strokes while minimally increasing the risk of major hemorrhage, especially intracranial hemorrhage. In two studies,\textsuperscript{29,30} the risk of intracranial hemorrhage was fairly low at INR values < 4.0 but was sharply higher at greater INR levels. Several studies\textsuperscript{29,33,37–39} have shown that the risk of bleeding while receiving oral anticoagulants increased among older patients. The risk of ischemic stroke is low down to INR values of 2.0. 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 evidence about whether this range should be changed for the very elderly (patients > 75 years old), who have both a higher risk of stroke and bleeding while receiving oral anticoagulants than younger patients.\textsuperscript{29,33,37–39} Suggested opinions from the literature for anticoagulation of very elderly patients include aiming for a target INR of 2.5 (range, 2.0 to 3.0) with especially close monitoring\textsuperscript{35} (which is consistent with our recommendation) or a target INR of 2.0 (range, 1.6 to 2.5).\textsuperscript{40,41}

**Risk Stratification in Patients With AF**

Numerous studies have demonstrated that OAC is very effective in decreasing the risk of stroke in patients with AF and that it is considerably more effective than daily aspirin. It is also clear that OAC is associated with a higher frequency of hemorrhage and is more inconvenient than aspirin. Each individual AF patient’s risk of stroke and hemorrhage must be considered when making the decision about the best antithrombotic preventive therapy.

The risk of stroke among AF patients not receiving anticoagulants has been studied in subjects participating in several of the randomized trials of antithrombotic therapy.\textsuperscript{6,42–45} The Atrial Fibrillation Investigators (AFI) group\textsuperscript{6} analyzed the data from the pooled control groups of the first five primary prevention trials and found the following independent risk factors for stroke in AF: prior stroke or TIA (relative risk [RR] = 2.5), age (RR = 1.6/decade), history of hypertension (RR = 1.6), and diagnosis of diabetes mellitus (RR = 1.7). In addition, patients < 80 years of age whose only stroke risk factor was coronary artery disease (previous MI or angina) had stroke rates of 4.6%/yr if not receiving anticoagulants. In essence, patients > 65 years old and/or those with any of these risk factors faced a substantial annual risk of stroke. This risk was lowered to about 1.5%/yr with adjusted-dose anticoagulant therapy. A subsequent AFI analysis\textsuperscript{43} of echocardiograms done in three of the original trials found that moderate-to-severe LV dysfunction was an additional strong risk factor (RR = 2.5). Left atrial diameter was not related to risk of stroke in AF.

The AFI analyses\textsuperscript{6} included data from the untreated control group of the SPAF-1 study.\textsuperscript{16} The SPAF Investigators recently published\textsuperscript{44} an analysis of risk factors for stroke among the 2,012 patients allocated to the aspirin arms of the SPAF-1, SPAF-2, and SPAF-3 randomized trials (in SPAF-3, aspirin was combined with very-low-intensity anticoagulation) and the SPAF-3 aspirin cohort study. Six features were found to be significant independent risk factors: prior stroke or TIA (RR = 2.9), age (RR = 1.8/decade), history of hypertension (RR = 2.0), systolic BP > 160 mm Hg (RR = 2.3), female gender (RR = 1.6), and alcohol consumption of ≥14 drinks/wk
controlled for, clinical trial data suggest that PAF confers an RR of stroke similar to constant AF. Patients with PAF tend to be younger and have a lower incidence of associated cardiovascular disorders than those with constant AF; therefore, their absolute stroke rate is lower. The RR provided by warfarin appears to be similar for patients with both PAF and constant AF. This conclusion, however, is limited by the relatively small number of patients (about 12% in the first five randomized trials) with PAF participating in the trials. Analyses of PAF are complicated by the fact that PAF patients differ greatly in the frequency and length of AF episodes. Studies of PAF are also limited by significant differences in patient awareness of their episodes of AF. The risk-benefit ratio for anticoagulation therapy in patients with PAF therefore remains imprecise. In patients with very infrequent and brief episodes of AF, the benefits of warfarin therapy may be offset by inconvenience and bleeding risks. In patients with frequent or prolonged paroxysms of AF, particularly those with stroke risk factors, warfarin therapy should be strongly considered.

The risk of stroke in patients with atrial flutter may be higher than previously assumed, as suggested in a retrospective analysis of 100 patients with atrial flutter. This assumption is also supported by the results of a study that evaluated the risk of thromboembolism in 191 consecutive unselected patients referred for treatment of atrial flutter, and documented an embolic event rate of 7% during 26 months of follow-up. These studies differ from earlier reports that found no risk of stroke or thromboembolism related to atrial flutter. To our knowledge, the role of anticoagulation therapy for patients with atrial flutter has not been evaluated in clinical trials; however, because these patients have a significant risk of developing AF, it may be reasonable to use similar antithrombotic therapies for stroke prevention.

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 developing AF. The prevalence of thyrotoxicosis in patients with AF is 2 to 5%. Some studies have reported a high frequency of stroke and systemic embolism in patients with thyrotoxic AF, although one study did not find a statistically significant difference when AF patients were compared to age- and sex-matched patients with normal sinus rhythm. Some of these studies have methodologic problems, which complicate interpretation of the results. Accordingly, available studies do not confirm 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 to be similar to other etiologies of AF, antithrombotic therapies should probably be chosen based on associated risk factors (see “Recommendations” section).

Left atrial size can be adequately assessed by transthoracic echocardiography, but other abnormalities of the left atrium can be seen via transesophageal echocardiography (TEE). While this modestly invasive approach is commonly used as an adjunct to elective cardioversion, it has also been applied to studies of outpatients with chronic
AF. Spontaneous echo contrast (a marker of stasis) and frank thrombi in the left atrium appear to confer a twofold to fourfold increase in risk of subsequent stroke. The vast majority (> 90%) of these thrombi involve or are confined to the left atrial appendage. Patients with TEE-detected aortic plaques with complex features (mobile, pedunculated, ulcerated, or ≥ 4 mm in diameter) had extremely high stroke rates in the SPAF-3 study. At present, there is no clear evidence that TEE findings add independently to risk stratification when clinical and transthoracic echocardiographic risk factors are considered.

Finally, studies have shown that AF patients with prosthetic heart valves (both mechanical and tissue valves) or rheumatic mitral valve disease are at high risk of stroke (see the chapters on valvular heart disease and prosthetic valves) and should be treated with adjusted-dose warfarin.

The purpose of risk classification schemes is to identify subgroups of patients with different risks of stroke: those in whom the risk of stroke is so high that warfarin is clearly indicated unless their risk of bleeding is very high, and those in whom the risk of stroke is sufficiently low that warfarin need not be used. Although there are groups of patients who clearly fall into these categories, there are also patients for whom the choice of warfarin vs aspirin is more difficult. Patients with AF who have at least one of the following risk factors are at high risk of stroke and should be offered OAC unless their risk of bleeding is high: previous stroke or TIA or systemic embolism, age > 75 years old, history of hypertension, prosthetic heart valve (mechanical or tissue valve), or rheumatic mitral valvular disease. Patients with poor LV systolic function also appear to be at high risk. The risk factor status is less secure in those age 65 to 75 years, in those with diabetes mellitus, and in those with coronary artery disease in the absence of LV dysfunction. However, we recommend anticoagulation if more than one of these “less severe” risk factors are present. Patients without cardiovascular disease or risk factors who are < 65 years old are at such low risk of stroke that they should be treated with aspirin alone. For patients who do not meet the high-risk or low-risk criteria, the absolute benefit of warfarin therapy is likely to be small. Treatment decisions should be individualized and consideration given to patient preferences and risk factors for bleeding.

Anticoagulation is a potentially risky therapy that imposes a variety of lifestyle constraints on patients. As a result, patient education and involvement in the anticoagulation decision is important. Many AF patients have a great fear of suffering a stroke and wish to take warfarin for a relatively small decrease in the risk of stroke, while others who are at relatively low risk for stroke will want to avoid the burdens and risks of anticoagulation and opt for aspirin. The safe use of anticoagulants depends on patient cooperation and a monitoring system that can achieve INR targets on a regular basis. The AFASAK-2 study demonstrates that anticoagulation at an INR of 2.0 to 3.0 can be quite safe even for elderly patients, and the study by Palareti et al demonstrates that low hemorrhage rates can be duplicated in clinical practice outside of trials, particularly if anticoagulation clinics are involved.

2. ANTICOAGULATION FOR ELECTIVE CARDIOVERSION

Synchronized capacitor discharge was introduced by Lown and coworkers for the rapid termination of atrial and ventricular tachyarrhythmias. Systemic embolism is the most serious complication of cardioversion and may follow direct current (DC), pharmacologic, and spontaneous cardioversion of AF.

2.1. AF

Bjerkelund and Orning performed a prospective cohort study in which cardioversion without anticoagulants resulted in a 5.3% incidence of clinical thromboembolism, whereas a 0.8% incidence of thromboembolism was noted in patients receiving OACs. Although this was not a randomized study, the results are compelling because the patients receiving anticoagulants were also at higher risk than those who were not. Several authors of case series also favor the use of adjusted-dose anticoagulation before cardioversion. Although sometimes occurring up to 10 days after cardioversion, the majority of these adverse events occur during the first 72 h after cardioversion and are presumed to be the result of thrombi present within the left atrium at the time of cardioversion. New thrombus may develop after DC cardioversion and highlights the importance of periconversion anticoagulation (see below). The duration of anticoagulation before cardioversion is not clearly defined, as the majority of these studies were retrospective analyses, but specific recommendations of 3 to 4 weeks of prophylactic adjusted-dose warfarin therapy before and after have been made by many investigators. In the recommendations that follow, clinical observations and the data from several of these studies are utilized.

The vast majority of data on cardioversion-related thromboembolism are based on electrical cardioversion. There are limited clinical data that have examined the issue of embolization after pharmacologic or spontaneous cardioversion of AF to sinus rhythm. Goldman reported that embolism occurred in 1.5% of 400 patients treated with quinidine for reversion of AF to sinus rhythm. This was similar to the 1.2% incidence of embolization that Lown reported in 450 electrical cardioversions in patients not receiving anticoagulants. Therefore, it seems prudent to administer anticoagulants to individuals undergoing pharmacologic cardioversion in a similar manner to those undergoing electrical cardioversion.

The mechanism of benefit conveyed by the month of warfarin treatment prior to elective cardioversion had previously been ascribed to the promotion of thrombus organization and adherence to the atrial wall. More recently, serial TEE studies of those presenting with new-onset AF and atrial thrombi on initial TEE have demonstrated resolution of the atrial thrombi after 1 month of warfarin treatment in the majority of subjects. It thus appears that the month of warfarin treatment may also facilitate “silent” thrombus resolution.
with increased risk for thrombus formation. Utilizing TEE, further depression of atrial appendage velocities, more intense left atrial spontaneous echocardiographic contrast, and even new thrombus formation have been described after external DC, internal DC, and even spontaneous cardioversion.\textsuperscript{75,76,81,84,85} 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.\textsuperscript{82–84} For this reason, adjusted-dose anticoagulation should be continued for 1 month after 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.

Therefore, for patients with AF, the following are recommended: (1) therapeutic warfarin (target INR 2.5; range, 2.0 to 3.0) anticoagulation should be given for 3 weeks before elective cardioversion; (2) anticoagulation should be continued for 4 weeks after successful cardioversion because it will decrease the likelihood that a fresh thrombus will form in the noncontractile left atrial appendage if the resumption of mechanical contraction is delayed, and it will decrease the formation of thrombus if AF recurs soon after successful cardioversion. For patients presenting with their first episode of AF, long-term anticoagulation beyond the first 4 weeks after cardioversion may be indicated if the patient has high clinical risk factors for stroke or is at high risk for recurrent AF (enlarged left atrium, significant LV dysfunction). If AF recurs, long-term (after 1 month) anticoagulation decisions should be based on the previously described clinical and echocardiographic criteria for chronic or paroxysmal AF.

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.\textsuperscript{75,76,81,84,85} While the detection of left atrial appendage thrombi is unreliable utilizing conventional transthoracic echocardiography, biplane and multiplane TEE have demonstrated very high accuracy\textsuperscript{86,87} 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 period. Data from several studies\textsuperscript{75,76,81,84,85} currently suggest rates of thromboembolism that are similar to those associated with standard therapy, with the advantages of an earlier recovery of atrial mechanical function, ease of anticoagulation management, elimination of the need for hospital readmission for elective cardioversion, and of cost-effectiveness if performed expeditiously and without a somewhat redundant transthoracic echocardiographic examination.\textsuperscript{88} Limitations of the TEE approach include patient discomfort, rare procedural complications, and limited availability at some centers.

Stroke has been described among patients who did not receive anticoagulation at the time of TEE or continued anticoagulation for a full month after cardioversion despite the absence of left atrial appendage thrombi on TEE.\textsuperscript{89–93} 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. Because of uncertainty regarding the role of TEE in guiding anticoagulant therapy at the time of electrical cardioversion, a large (>1,000 patients) randomized multicenter international study, Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE), comparing conventional vs the novel TEE approach is currently underway. The results of the ACUTE pilot study\textsuperscript{95} comparing TEE-guided cardioversion with standard management of cardioversion in AF patients have been reported. Sixty-two of 126 patients who had AF lasting >48 h were randomly selected to receive TEE-guided cardioversion. TEE was performed in 56 patients, and atrial thrombi were found in 7 patients. Cardioversion was successful in 38 of 45 patients who had early cardioversion. There were no embolic events in the patients who were free of left atrial thrombus. There was one embolic event (1.6%) occurring 3 days after cardioversion in a patient randomized to the conventional management group. Though cardioversion occurred earlier in the TEE-guided group, there was no difference in the likelihood of sinus rhythm at 8 weeks after cardioversion.

For AF of short duration (<48 h), the usual clinical practice is to perform cardioversion without TEE or prolonged precardioversion anticoagulation. This practice was called into question when a study\textsuperscript{94} reported a 13% prevalence of atrial thrombi on TEE among patients with AF of <72 h duration. Subsequently, however, data were reported from a study\textsuperscript{95} of 357 patients who had a symptomatic duration of AF for <48 h. Two hundred fifty patients converted spontaneously, and 107 underwent pharmacologic or electrical cardioversion, all without screening TEE or a month of warfarin treatment prior to cardioversion. Clinical thromboembolism occurred in three subjects (<1%), all of whom were elderly woman without a history of prior AF and with normal LV systolic function. Preliminary data from the Canadian AF Registry\textsuperscript{94,96} also suggest a very low incidence of adverse events if these patients undergo early cardioversion. Although safe in these studies, it may be prudent to perform TEE or delay cardioversion for 1 month for very high-risk patients (eg, patients with a history of prior stroke/thromboembolism or severe LV systolic dysfunction).

While patients with short-duration AF (<48 h) may not require TEE or a month of prolonged warfarin treatment prior to cardioversion, it may be prudent to initiate heparin anticoagulation at presentation. Many of these patients will require anticoagulation after cardioversion, and the use of heparin will further decrease the likelihood of new thrombus formation during the pericardioversion period.
Anticoagulation for Emergency Cardioversion of AF Patients

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. The role of anticoagulation in these circumstances remains controversial, but heparin therapy at the time of cardioversion may be useful to prevent thrombi from forming due to further atrial appendage dysfunction after cardioversion.

2.2. Atrial Flutter and Supraventricular Tachycardia

In several published series97–100 of patients who underwent cardioversion, all three arrhythmias (AF, atrial flutter, and supraventricular tachycardia) were pooled together when the data were analyzed. Therefore, it is difficult to estimate the risk of embolism during cardioversion for atrial flutter. However, there have been several reports50,51,97–99,101 of embolization after cardioversion of patients with pure atrial flutter. Patients at particularly high risk include those with valvular heart disease, prior thromboembolism, congestive heart failure, and LV systolic dysfunction. Whether these patients had unrecognized episodes of AF or spontaneous echo contrast is unknown.99 Similar to AF, delayed restoration of atrial function after cardioversion from atrial flutter has been described.102 These findings raise concern that patients with atrial flutter are at increased risk of embolization at the time of cardioversion. Consideration should be given to treating patients with atrial flutter in the same manner as patients with AF at the time of cardioversion, especially those with a history of prior AF or thromboembolism, or LV systolic dysfunction.101,103 Although some retrospective studies50,101 have suggested an increased risk of stroke and thromboembolism in patients with sustained or intermittent atrial flutter, more information is required before a firm recommendation can be made about long-term OAC therapy in these patients.

Recommendations

1. Efficacy of Long-term Antithrombotic Therapy in AF

Recommended Therapy

For patients with any high-risk factor or more than one moderate-risk factor, we recommend warfarin (target INR 2.5; range, 2.0 to 3.0). See chapter “Antithrombotic Therapy in Patients With Mechanical and Biological Prosthetic Heart Valves” for target INRs in patients with mechanical heart valves. For patients with one moderate-risk factor, we recommend aspirin, 325 mg/d, or warfarin (target INR 2.5; range, 2.0 to 3.0). For patients with no high-risk factors and no moderate-risk factors, we recommend aspirin, 325 mg/d.

Risk Stratification

High-risk factors include prior stroke/TIA or systemic embolus, history of hypertension, poor LV systolic function, age > 75 years, rheumatic mitral valve disease, and prosthetic heart valve. Moderate-risk factors (factors for stroke that have been identified in AF patients in various studies but are not as strong or consistent as the high-risk factors listed above) include age 65 to 75 years, diabetes mellitus, and coronary artery disease with preserved LV systolic function.

High-Risk Patients

1.1. We recommend the use of adjusted-dose warfarin anticoagulation (target INR 2.5; range 2.0 to 3.0) rather than aspirin in patients with AF at high risk for ischemic stroke because it markedly decreases the risk of ischemic stroke in patients with AF (grade 1A).

1.2. For high-risk patients, we recommend that clinicians offer aspirin therapy if adjusted-dose warfarin is contraindicated or declined by the patient and if there are no contraindications to aspirin (grade 1A).

1.3. We recommend that clinicians do not use aspirin plus low-fixed-dose warfarin therapy (grade 1A).

1.4. Although to our knowledge no randomized trials of OAC have been undertaken in AF patients with rheumatic mitral valve disease or prosthetic heart valves (mechanical or tissue valves), we recommend that clinicians use OAC in these patients (grade 1C+).

Low-Risk Patients

1.6. We recommend that patients with AF who are < 65 years with no clinical or echocardiographic evidence of cardiovascular disease should be treated with aspirin (grade 2C).

Moderate-Risk Patients

1.7. Some AF patients will have a risk of stroke that is between that of the high-risk and low-risk groups mentioned. For these patients, the absolute stroke RR of warfarin vs aspirin is likely to be small. We recommend the use of either OAC or aspirin for patients with one of these moderate risk factors (grade 1A in comparison to no treatment).

1.8. Patients with more than one of these moderate-risk factors are at higher risk of stroke than are those with only one risk factor, and we recommend to
treat these patients in the same manner as high-risk patients (see above; grade 2C).

The ultimate choice of therapy depends on many factors, including the clinician’s assessment of the magnitude of the patient’s risk (eg, whether the patient has single or multiple risk factors), the ability to provide high-quality monitoring of the intensity of OAC, the patient’s risk of bleeding with OAC, and patient preference.

2. ANTICOAGULATION FOR ELECTIVE CARDIOVERSION

2.1. AF

2.1.1. We recommend that clinicians administer oral anticoagulant therapy (target INR 2.5; range 2.0 to 3.0) for 3 weeks before and at least 4 weeks after elective DC cardioversion of AF patients (grade 1C+).

2.1.2. Alternatively, we recommend that AF patients undergo anticoagulation then undergo TEE, and have cardioversion performed without delay if no thrombi are seen (grade 1C). For these patients, adjusted-dose warfarin therapy should still be continued until normal sinus rhythm has been maintained for at least 4 weeks.

2.1.3. Although data are limited, the risk of embolism following cardioversion in patients who have been in AF for < 48 h appears to be low. However, we recommend the use of anticoagulation during the pericardioversion period (grade 2C).

2.2. Atrial Flutter and Supraventricular Tachycardia

2.2.1. We recommend that clinicians manage OAC at the time of cardioversion in patients with atrial flutter in a manner similar to that used for AF (grade 2C).

2.2.2. In the absence of prior thromboembolism, we do not recommend antithrombotic therapy for cardioversion of supraventricular tachycardia (grade 2C).

Treatment of potential precipitants of AF (ie, thyrotoxicosis, pneumonia, congestive heart failure) should be completed prior to attempting elective DC cardioversion.

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