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CLINICAL SURVEY

Antithrombotic treatment in patients with atrial fibrillation as a risk factor of stroke

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Abstract: For over two decades, valuable insights have been accumulated from epidemiologic studies and randomized trials about the risks and prevention of atrial fibrillation. Atrial fibrillation (AF) substantially raises the risk of stroke, most likely through an atrio-embolic mechanism. Warfarin and other members of its class of oral anticoagulants targeted at an international normalized ratio (INR) of 2.5 can abrogate the risk of stroke attributable to AF effectively and fairly safely. High-quality management of anticoagulation can be achieved in usual clinical care. These insights have important implications for the care of individual patients and more generally for public health. Future research is needed to specify the risk of stroke and hemorrhage among patients with AF better, particularly among older individuals, to optimize use of antithrombotic agents, and to define the role of recently developed antithrombotic drugs and invasive nondrug approaches *(Tab. 3, Ref. 20).*
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Key words: atrial fibrillation, stroke, heart failure, antithrombotic treatment.

AF is a powerful risk factor for thromboembolism, raising the risk of ischemic stroke fivefold. Because AF is common among older people, who are at higher stroke risk, it can be estimated that approximately 14 % of all strokes in the United States are attributable to AF. With the projected aging of the US population, the number of individuals with AF will rise, and prevention of stroke caused by AF will become an even more important public health concern. The predominant mechanism of AF-related ischemic stroke appears to be thromboembolism, from the left atrium (LA). AF results in a loss of effective atrial contraction, leading to relative stasis of blood and thrombus formation. In nonvalvular AF, the left atrial appendage is the main site for such intracardiac thrombi. Research conducted over the past 15 years has demonstrated that oral anticoagulants are highly effective in reducing the risk of stroke in AF, presumably by preventing left atrial appendage thrombi.

Efficacy of oral anticoagulants for stroke prevention in atrial fibrillation

Multiple high-quality, randomized trials provided consistent evidence for the remarkable efficacy of long-term anticoagulation in preventing stroke associated with AF (1–5). The earliest trials compared oral anticoagulants to no antithrombotic therapy. These trials included five primary prevention studies, AFASAK-1 (First Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation Study), BAATAF (Boston Area Anticoagulation Trial for Atrial Fibrillation), SPAF I (Stroke Prevention in Atrial Fibrillation), CAFA (Canadian Atrial Fibrillation Anticoagulation Study), and SPINAF (Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation) and the secondary prevention European Atrial Fibrillation Trial (EAFT). All of the primary prevention studies except CAFA were stopped before their planned termination date, because anticoagulation was convincingly more effective than control. CAFA was stopped early because of the efficacy observed in other trials. Lead investigators of the first five primary prevention trials pooled their individual patientlevel data to provide a more precise estimate of the efficacy of anticoagulation and to allow identification of risk factors(6). Several of the first North American trials used prothrombin time ratio target anticoagulation intensities rather than INRs, because INR assessments were not available at the onset of these trials. Anticoagulants were shown to dramatically reduce the risk of stroke, with a pooled relative risk reduction of 68 % (95 % confidence interval (CI) 50 %, 79 %) (Tab. 1). The absolute reduction in risk was 3.1 % per year, with a 4.5 % annual stroke rate in control patients compared with 1.4 % in anticoagulated patients. Anticoagulants also significantly reduced the rate of all-cause mortality by 33 % (95 % CI 9 %, 51 %). The rates reported in the pooled analysis were calculated according to the standard intention-to-treat principle. In fact, most ischemic strokes among subjects randomized to anticoagulant therapy occurred after anticoagulation had been stopped or during periods

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when anticoagulation intensity was below target. It can be inferred that anticoagulation at target intensity can reduce the risk of stroke by approximately 80 %. Because AF increases the risk of stroke by fivefold, anticoagulation at target intensity thus can remove nearly all of the stroke risk attributable to AF. These trials used a wide range of target intensities of anticoagulation; the BAATAF and SPINAF trials used the relatively low- intensity target prothrombin time ratio of 1.2–1.5 that was proven to work in preventing deep venous thromboembolism (7). The efficacy of warfarin in these trials using lower target intensities of anticoagulation was comparable to those with higher intensity targets. Anticoagulation appeared effective in all subgroups of patients, including the 207 patients with intermittent AF, with a 1.7 % annual stroke rate in the anticoagulation arm compared with 5.7 % in the controls. Overall, the rate of major hemorrhage was low in these trials, 1.3 % per year in the anticoagulant arm versus 1.0 % per year in the control. The relative efficacy of anticoagulation in the EAFT secondary prevention trial was strikingly consistent with the results from the primary prevention trials, although the absolute rate of stroke was threefold higher in high-risk EAFT patients. EAFT (8) studied patients with nonvalvular AF who had experienced a transient ischemic attack (TIA) or minor ischemic stroke within 3 months of entry to the trial. Two-hundred and twenty five patients were randomized to oral anticoagulation with acenocoumarol or phenprocoumon (INR target 2.5–4.0), and 214 were randomized to placebo. There was a 3.9 % annual event rate in the anticoagulation arm compared with a 12 % rate in the placebo arm, for an intent-to-treat relative risk reduction of 66 % (95 % CI 43 %, 80 %).

Adjusted-dose anticoagulation compared with low-intensity anticoagulation

The initial trials demonstrated that anticoagulation achieving INR levels primarily in the 2.0–3.0 range was effective and acceptably safe. A natural next step was for trials to explore the lowest effective intensity of anticoagulation so as to minimize risk of hemorrhage. The SPAF III study (9) was the most informative of these trials. The second trial in the SPAF series, SPAF II (10) had observed a high intracranial hemorrhage rate of 1.8 % per year among patients older than 75 years. At least some of this toxicity was attributable to the high target intensity of anticoagulation used in SPAF II (INR 2.0 to 4.5). SPAF III was crafted to test whether very low intensity anticoagulation (INR 1.2 to 1.5) combined with aspirin (325 mg per day could prevent ischemic stroke in older high-risk AF while diminishing hemorrhagic risk. This was a large trial randomizing 523 patients to adjusted-dose warfarin (target INR 2.0 to 3.0) and 521 patients to low-intensity fixed-dose warfarin plus aspirin. This trial was stopped early because of the demonstrated superiority of adjusted-dose warfarin. After a mean follow-up period of 1.1 years, there were 11 events in the adjusted-dose warfarin arm compared with 44 events in the lowintensity warfarin plus aspirin arm, for a relative risk reduction of 74 % (95 % CI 50 %, 87 %). This relative risk reduction was essentially the same as that reported from the first five primary prevention trials comparing warfarin to no antithrombotic therapy. Additionally, there was no reduction in rate of major hemorrhage, including intracranial hemorrhage, in the low-intensity anticoagulation plus aspirin group, addressing some of the concerns about bleeding risk raised by SPAF II. SPAF III added substantially to the evidence supporting anticoagulation targeted at INR 2.0–3.0 for patients at significant risk of AF-related stroke. Several subsequent trials addressed the efficacy of low-intensity anticoagulation in AF (11–13). These included the AFASAK-2 (11) and the Minidose Warfarin in Nonrheumatic Atrial Fibrillation (12) trials, both of which compared fixed low-dose warfarin (1.25 mg per day) to warfarin targeted at INR 2.0 to 3.0. Both trials stopped early because of the findings of SPAF III and generated largely indeterminate results because of their low statistical power. The PATAF (Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation) Study (13) randomized patients eligible for anticoagulation to adjusted-dose coumarin (target INR 2.5 to 3.5), low-intensity coumarin (INR 1.1 to 1.6), or aspirin. The low annual event rate of 1% in this trial hampered meaningful comparisons.

Efficacy of aspirin and other antiplatelet agents

In addition to comparing anticoagulation with placebo, the AFASAK-1, SPAF I, and EAFT studies also included aspirin arms at doses of 75 mg, 325 mg, and 300 mg per day respectively. Interest in aspirin was spurred by SPAFI, which reported a 42 % reduction in event rate, although AFASAK-1 and EAFT (14) reported event rates in the aspirin arms similar to those in placebo arms. The SPAF I assessment of aspirin was composed of two separately randomized groups of patients. The first group consisted of 210 warfarin-eligible patients who were randomized to open-label warfarin (prothrombin time ratio of 1.3 to 1.8). An additional 206 patients were randomized to aspirin (325 mg per day), and 211 were randomized to aspirin-placebo. The second group contained patients who were not considered candidates for anticoagulation. Reasons for warfarin ineligibility included patient/physician preference, high risk of hemorrhage, lone AF, and for most of the enrollment period, age over 75 years. Within this second group, 346 patients were randomized to aspirin, and 357 were randomized to placebo. The efficacy of aspirin versus placebo in these two subtrials was distinctly different. In the older group 2 subtrial, the estimated efficacy of aspirin was a nonsignificant 8 %. In the group 1 subtrial studying younger patients, however, the observed efficacy was 94 %. Thus, even within SPAF I, the evidence supporting aspirin's efficacy was highly inconsistent. The pooled analysis of the AFASAK-1, EAFT, and SPAF I trials reported an overall efficacy for aspirin of 21 %, with the lower bound of the confidence interval for this estimate including 0 % (Tab. 1). Two meta-analyses at the trial level differed on their assessment of the statistical significance of aspirin's efficacy, depending on whether the heterogeneity of results in the two subtrials of SPAF I formally was taken into account. In sum, these trials comparing aspirin with placebo make clear that aspirin's efficacy is small, at best. Aspirin is not the

Tab. 1. Efficacy og oral anticoagulation and aspirin for AF from patient – level meta-analysis of pooled data of randomized trials (89).

Treatment comparisons	Number of subjects	Relative risk reduction and 95% confidance interval*
Adjusted-dose oral anticoagulation versus no	1225	68% (50%, 79%)
Antithrombotic therapy (11)	1236	21% (0%, 38%)
Aspirin versus no antithrombotic therapy	1292 1282	
Adjusted-dose orale anticoagulation versus aspirin (26)	1939 2113	52% (37%, 63%)

*Relative risk reduction in ischemic stroke. Trials in each analysis are not identical

only antiplatelet agent that has been tested in AF. The SIFA (Studio Italiano Fibrillazione Atriale) (15) trial assessed the efficacy of indobufen, a reversible inhibitor of cyclooxygenase activity, randomizing 462 patients to indobufen (200 mg twice daily) and 454 patients to adjusted-dose warfarin (target INR 2.0–3.5). The primary outcome was combined incidence of vascular events, which included stroke, myocardial infarction, systemic or pulmonary embolism, and vascular death at the planned study duration of 1 year. There was no statistically significant difference between warfarin and indobufen with regards to the combined outcome (49 events in the indobufen arm and 41 events in the warfarin arm). There were eight major hemorrhages in the warfarin arm compared with one in the indobufen arm. These results have not yet been replicated.

Efficacy of aspirin compared with oral Anticoagulation

The most powerful assessments of the efficacy of anticoagulation and of aspirin were provided by trials comparing these agents with placebo. Several randomized trials also directly compared aspirin with anticoagulation. In aggregate, these studies provide a reasonably precise comparison of the efficacy of aspirin versus adjusted-dose anticoagulation. A meta-analysis using pooled individual patient-level data from the AFASAK 1 and 2; EAFT, SPAF I, II, III; and PATAF trials found that anticoagulants were significantly more effective than aspirin in decreasing the rate of all strokes, with a hazard ratio (HR) of 0.55 (95 % CI 0.43 to 0.71), and ischemic stroke (HR 0.48 (95 % CI 0.37 to 0.63)) and cardiovascular events (HR 0.71 (95 % CI 0.59 to 0.85)). Trials using ineffective doses of anticoagulation combined with aspirin were included in the pooled aspirin arm of this analysis. Anticoagulation was associated with a higher risk of major hemorrhage compared with aspirin (HR 1.71 (95 % CI 1.21 to 2.41)). Overall, this meta-analysis estimated that treatment with oral anticoagulants versus aspirin would prevent 23 ischemic strokes per 1000 patients per year while causing nine major bleeding events. Both this meta-analysis and a more recent and powerful assessment of stroke outcome in AF make clear that disabling, presumably embolic, strokes are prevented far better by adequate anticoagulation than by lowintensity anticoagulation or aspirin. Thus, not only does anticoagulation above INR 2.0 prevent more strokes than aspirin, but it also appears superior for preventing disabling or fatal strokes. In summary, randomized trials have demonstrated that oral anticoagulants are significantly and substantially more effective than both placebo and aspirin in the prevention of stroke for AF (Tab. 1). Although data exist supporting a modest efficacy of aspirin in AF, these data are far less consistent than those supporting oral anticoagulation. Moreover, aspirin appears to be less effective in preventing the most severe strokes.

Anticoagulation combined with antiplatelet agents

Trials testing the combination of aspirin with very low levels of anticoagulation did not show this approach to be effective in the prevention of stroke. In contrast, the recent NASPEAF trial (National Study of Prevention of Embolism in Atrial Fibrillation) assessed the efficacy of the cyclooxygenase inhibitor triflusal (600 mg per day, roughly equivalent to aspirin at 300 mg per day) in combination with near-standard intensity oral anticoagulation (target INR 1.5 to 2.4) versus anticoagulation targeted at the standard INR of 2.0 to 3.0. Preliminary reports of the study indicated that the combination of antiplatelet agent plus modestly reduced-intensity anticoagulation (mean INR roughly 2.0) was actually superior to standard anticoagulation at INR 2.0 to 3.0. These observations certainly bear replication. Aspirin is highly recommended for the prevention of CAD. Whether patients with both AF and CAD should receive both aspirin and full-dose anticoagulants has not been studied formally. Cardiology guidelines suggest adding aspirin (81 mg per day) to anticoagulants (INR 2.0–3.0) for patients with AF and CAD or diabetes (16). The core issue is whether addition of aspirin provides greater protection against coronary disease than that provided by anticoagulation alone, and whether the combination substantially increases the risk of serious bleeding. Studies in patients with coronary disease (primarily without AF) suggest that anticoagulation at intensities generally higher than those used for AF is quite protective. Further, the pooled analysis comparing aspirin with anticoagulants in patients with AF indicates anticoagulation alone is at least as effective as aspirin alone in the prevention of MI. In contrast, the previously described NASPEAF study suggests that combination therapy may be superior even for stroke prevention. No trials have studied patients withAF and CAD specifically. The authors suspect that anticoagulation at INR 2.0–3.0 alone is quite similar to anticoagulation at this intensity plus 81 mg per day of aspirin in preventing both ischemic stroke and coronary artery events. For those anticoagulated AF patients at very high risk of coronary events, it might be worth adding aspirin in addition to warfarin.

Risk-stratification for atrial fibrillation

Oral anticoagulants increase the risk of hemorrhage and can be inconvenient to monitor and manage. Several risk-stratification schemes have emerged to better distinguish which patients with AF benefit most from anticoagulation. These schemes were based mostly on post hoc analyses of randomized trials or observational studies. The Atrial Fibrillation Investigators pooled analysis (Tab. 2) identified the following clinical factors as independent risk factors for stroke: increasing age (relative risk (RR) = 1.4 per decade), previous stroke/TIA (RR=2.5), history of hypertension (RR=6), and diabetes mellitus (RR=1.7). Patients younger than 65 years without the previously described risk factors were at low risk for stroke, with an annual event rate of 1.0 % (95 %, CI 0.3 to 3.1). This rate was comparable to the 1.0 % (95 % CI 0.3 to 3.0) event rate on warfarin. Analysis of echocardiographic data from three of the trials found that moderate-to-severe left ventricular systolic dysfunction was also an independent risk factor for stroke (RR=2.5). The SPAF investigators developed a risk-stratification scheme based on data from 2012 participants in the SPAF I, II, and III trials (Tab. 2). Study participants who were on aspirin or low-dose warfarin were included in the analysis. Prior stroke or TIA was a strong independent predictor of future stroke (RR=2.9). When the analysis was restricted to patients without prior history of stroke (ie, primary prevention), independent risk factors for stroke included increasing age (RR=2.0 per decade) and history of hypertension (RR=2.2). The SPAF analysis noted that women over age 75 were at particularly high risk, as were patients with systolic blood pressures of greater than 160 mmHg. Both analyses found that subjects characterized as having intermittent (or paroxysmal) AF faced the same stroke risk as those with sustained AF, given the same risk factors, and derived similar benefit from anticoagulant therapy. Although these risk-stratification schemes identified similar clinical factors that predicted a higher risk for stroke, there was significant variation when the three schemes were applied to both a longitudinal cohort of patients who had participated in the SPAF III trial and to a cohort of 13,559 AF patients enrolled in a large health maintenance organization (HMO). More discriminatory means of risk stratification are needed. Transesophageal echocardiography (TEE) can visualize the LA and its appendage. Presence of clot and markers of left atrial stasis are strong predictors of stroke risk among patients with AF. Although TEE has a role in guiding anticoagulation peri-cardioversion, it is probably not acceptable as a periodic test to stratify risk in the usual management of AF.

Bleeding complications associated with Anticoagulation

Hemorrhage is the most significant complication associated with anticoagulant therapy. The primary risk factors for hemorrhage while on oral anticoagulants are increasing age and anticoagulant intensity. The rate of major hemorrhage in the pooled analysis was 1.3 % per year in the warfarin arm compared with 1.0 % in the control arm. Table 3 presents the hemorrhagic event rates observed in each of the randomized trials. Because patients enrolled in randomized studies are a selected population and undergo more intensive monitoring of anticoagulation, hemorrhage rates in the real-world setting may differ. Several observational studies have delineated the incidence of major hemorrhage in anticoagulated patients further. In one Netherlands-based study, where outpatient anticoagulation was managed by centralized

Tab. 2. Annual rates of ischemic stroke in AF by risk group from the Atrial Fibrillation Investigators (AFI) pooled analysis and SPAF investigators pooled analysis.

AFI risk category	AFI pooled analysis		SPAF investigators	
	Control	Warfarin	Aspirin	
	Annual rate (95% CT)	Annual rate (95% CT)	SPAF risk category	Annual rate (95% CT)
Age <65 years			Primary	0.9 (0.6–1.6)
no risk factors	1.0 (0.3–3.1)	1.0 (0.3–3.0)	prevention	
≥1 risk factor	4.9 (3.0–8.1)	1.7 (0.8–3.9)	low risk	
Age <65–75 years			Moderate	2.6 (1.9–3.6)
no risk factors	4.3 (2.7–7.1)	1.1 (0.4–2.8)	risk	
≥1 risk factor	5.7 (3.9–8.3)	1.7 (0.9–3.4)	High risk	7.1 (5.4–9.5)
Age <75 years			Secondary	13 (7.8–18)
no risk factors	3.5 (1.6–7.7)	1.7 (0.5–5.2)	prevention	
≥1 risk factor	8.1 (4.7–14)	1.2 (0.3–5.0)	(prior troke or TIA)	

*AFI Risk Factors include history of hypertension, diabetes, and prior stroke or transient ischemic attack (TIA). SPAF primary prevention risk factors. High risk factors include women older than 75 years, age over 75 years plus history of hypertension, and systolic blood pressure >160 mmHg. Moderate risk factors are history of hypertension plus age 75 years, and diabetes. Low risk subjects are those without high or moderate risk factors. Primary prevention refers to patients without a history of prior stroke or TIA.
*CI, confidence interval; SPAF, stroke prevention in AF.

Tab. 3. Annual rates of major hemorrhage and intracranial hemorrhage in randomized trials of anticoagulation for AF.

Study	No of pts	Major hemorrhage		Intracranial hemorrhage	
		No of events	Annual rate	No of events	Annual rate
AFASAK-1					
Warfarin	335	a	a	a	a
Aspirin	336	a	a	a	a
Placebo	336	a	a	a	a
BAATAF					
Warfarin	212	2	0.4 % b	1	0.2 % b
Control	208	1	0.2 % b	0	0.0 % b
SPAF 1					
Warfarin	210	4	1.5 %	2	0.8 %
Aspirin (groups 1 and 2)	552	10	1.4 %	2	0.3 %
Placebo (groups 1 and 2)	568	14	1.9 %	2	0.3 %
CAFA					
Warfarin	187	5	2.5 %	1	0.4 % b
Placebo	191	1	0.5 %	0	0.0 % b
SPINAF					
Warfarin	260	7	1.5 % b	1	0.2 % b
Placebo	265	4	0.9 % b	0	0.0 % b
EAFT					
anticoagulation	225	13	2.8 %	0	0.0 % b
Aspirin (groups 1 and 2)	404	6	0.9 %	2	0.5 % b
Placebo (groups 1 and 2)	378	40	7 %	1	0.1 % b
SPAF II (age=75 years)					
Warfarin	358	a	1.7 %	6	0.5 %
Aspirin	357	a	0.9 %	3	0.2 %
SPAF II (age >75 years)					
Warfarin	197	a	4.2 %	7	1.8 %
Aspirin	188	a	1.6 %	3	0.8 %
SPAH III					
Standard-dose warfarin	523	12	2.1 %	3	0.5 %
Fixed low-dose warfarin plus aspirin	521	13	2.4 %	5	0.9 %
SIFA					
Warfarin	454	8	1.8% b	4	0.9 % b
Indobufen	462	1	0.2% b	1	0.2 % b
AFASAK-2					
Warfarin	170	4	1.1 % b	2	0.6 % b
1.25 mg/day warfarin	167	3	0.8 % b	1	0.3 % b
1.25 mg/day warfarin plus aspirin	171	1	0.3 % b	0	0.0 % b
aspirin	169	5	1.4 % b	1	0.3 % b
Pengo el al.					
Warfarin	153	4	2.6%	1	0.6 % b
1.25 mg/day warfarin	150	1	1.0%	0	0.0 % b
PATAF					
Coumarin	131	2	0.5 %	1	0.3 % b
Low-intensity coumarin	244	10	1.4 %	4	0.6 % b
Aspirin	319	11	1.4 %	8	1.0 % b
Japanese NVAFESPC					
Warfarin	55	6	6.6 %	3	3.3 % b
Low-intensity warfarin	60	0	0.0 %	0	0.0 % b
FFAACS					
Fluindione plus aspirin	76	3	4.8 %	0	0.0 %
Fluindione plus placebo	81	1	1.4 %	0	0.0 %

*a Information not available in original manuscript, *b Annual rates calculated from numbers of events and estimated person-year published in original report.

thrombosis services, the annual rate of major hemorrhage (defined as intracranial hemorrhage, fatal bleeding, requiring blood transfusion, hospital admission, or surgery, and muscle or joint bleeding) was 2.7 per 100 person years (17). Risk factors for major hemorrhage included increasing age, with each 10-year increase in age associated with 46 % more bleeding compared with patients younger than age 40. In another study, a prospective inception-cohort of 2745 patients followed in Italian anticoagulation clinics, the rate of major hemorrhage (defined M.C. Fang, D.E. Singer: Cardiology Clin 22 (2004) 47–62 53 as fatal, intracranial, ocular, articular, retroperitoneal, surgical/angiographic intervention, hemoglobin reduction of at least 2 g/dL, or transfusion of at least two blood units) was 1.1 per 100 person years. Risk factors for hemorrhage were age of at least 70 years, indication for anticoagulation, and increased INR. A cohort study from Fihn et al (18) found risk factors for first episode of hemorrhage to be increasing anticoagulant intensity, shorter duration and variability of anticoagulation, and three or more comorbid conditions Increasing age was not found to be a significant risk factor for major hemorrhage. Intracranial hemorrhage, perhaps the only hemorrhagic complication equivalent to ischemic stroke in severity, is particularly challenging to study in a prospective fashion because of its low incidence. In the pooled analyses of the five primary prevention trials, there were only 10 intracranial hemorrhages, for an annual rate of 0.4 %. Large, nontrial, observational studies have been very useful in identifying risk factors for intracranial hemorrhage on warfarin. Such risk factors include increasing age, increasing anticoagulant intensity, cerebrovascular disease, and hypertension. Cerebral amyloid angiopathy and cerebral leukoaraiosis also have been linked to intracranial hemorrhage. Fear of hemorrhage has been cited as the major reason physicians avoid using long-term anticoagulant therapy for patients. This concern is even more prominent when deciding to use anticoagulation therapy in elderly patients. More precise techniques of risk-stratification such as with genetic testing may improve the assessment of hemorrhage risk in the future. In the meantime, centralization and coordination of patients' anticoagulation using dedicated anticoagulation clinics may help standardize the management and monitoring of patients.

Appropriate anticoagulation intensity

Lower-intensity anticoagulation at target INRs substantially less than 2.0 are not effective in preventing ischemic stroke. Assessment of narrower ranges of INR by randomized trials is challenging because of low event rates on anticoagulation, and because maintaining INRs within a specific range is difficult. By contrast, large observational studies have been able to provide important information regarding the optimal intensity of anticoagulation. In one casecontrol study, INRs above 2.0 were not associated with any additional protective effect on stroke risk. The stroke risk rose significantly at INRs less than 2.0, however; at INR 1.7, the odds of stroke doubled. At INR 1.5, the stroke risk tripled. Other observational studies indicate that risk of intracranial hemorrhage does not increase substantially until INR levels near 4.0. Because increasing anticoagulant intensity is a strong risk factor for hemorrhage, recent guidelines by the ACC/AHA/ESC have suggested using a lower target INR range for a subgroup of patients over the age of 75 without prior history of stroke. Further investigation as to how effective this strategy is at reducing stroke and hemorrhage remains to be seen. It is unclear whether lowered INRs substantially protect against intracranial hemorrhage, whereas patients with INRs less than 2.0 who develop ischemic stroke have significantly higher mortality rates than those with higher INRs. For now, optimal anticoagulation intensity for AF appears to be between INR 2.0 and 3.0.

Stroke prevention in atrial fibrillation in actual clinical practice

Although the results of the randomized trials of anticoagulation for AF were dramatic, translation of these findings to usual clinical practice is not necessarily straightforward. Only a small fraction of apparently eligible patients actually entered the initial trials, and presumably, the patients enrolled were particularly good candidates for anticoagulation. The net benefit of anticoagulation for AF might be diminished in usual clinical practice, where patients are less highly selected, and control of anticoagulation intensity might be inferior to that achieved in the trials. A recent clinically detailed analysis of a cohort of 13,559 patients with AF enrolled in Kaiser Permanente of Northern California, however, observed that the efficacy of anticoagulation translated well into usual clinical care. Warfarin therapy was associated with a 53 % lower rate of thromboembolism, and rates of major hemorrhage were quite low. Thus, well-organized management of anticoagulation for patients with AF can reduce rates of stroke substantially and relatively safely in actual clinical practice. Use of anticoagulants for AF was uncommon before the initial randomized trials, but over the past decade, the core message of the trials has been disseminated widely to physicians and patients and incorporated into several sets of guidelines. Use of warfarin for AF has increased steadily, such that roughly 50 % of patients with AF in the United States are taking anticoagulants. The largest increase was observed in the most elderly patients. Roughly a third of patients with AF are 80 years or older, and the size of this group will increase markedly over upcoming decades. In general, these patients have the greatest risk for ischemic stroke without anticoagulation and the greatest risk for major hemorrhage (especially intracranial hemorrhage) on anticoagulants. The absolute net balance seems to strongly favor use of anticoagulants in these older patients. It must be noted, however, that the initial trials included relatively few patients older than 80 years. Careful study of the outcomes of elderly patients with AF remains especially important.

Management of anticoagulation

Outpatient monitoring and management of oral anticoagulants can be inconvenient for patients and physicians. Special-

ized anticoagulation clinics can help standardize anticoagulant use. Although such clinics appear to improve the time patients spend in the target anticoagulant intensity range moderately, there have been few direct comparisons of anticoagulation clinics to usual care. One multi-center randomized trial in six large managed care organizations randomized practice clusters to having access to an anticoagulation clinic versus no access (19). The primary outcome was the proportion of time that the INR was within the target range. This trial did not show significant differences between usual care and access to an anticoagulation clinic, although the proportion of time control patients spent in their target INR range was substantially more than that reported in prior community studies (20). Alternative means of monitoring include patient self-management of anticoagulation. In one small randomized, cross-over study based in the Netherlands (141), home monitoring and selfadjustment of oral anticoagulants were at least as good as a centralized anticoagulation service. Although expensive, home monitors can allow patients to adjust their anticoagulation more frequently and conveniently.

Conclusion

Risk-stratification schemes have been incorporated into several guidelines, including the Sixth Consensus Conference on Antithrombotic Therapy of the American College of Chest Physicians Consensus (ACCP). High-risk patients were categorized as those with a history of prior stroke, TIA, or systemic embolus, hypertension, poor left ventricular function, age older than 75 years, or rheumatic mitral valvular disease. Patients at moderate risk were those aged 65 to 75 years or patients with diabetes or CAD. Adjusted-dose warfarin was recommended for high-risk patients and could be considered for patients with multiple moderate risk factors. Patients younger than 65 and with no clinical or echocardiographic evidence of cardiovascular disease were at low-risk for stroke and could take aspirin alone. The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines differ modestly. These guidelines recommend anticoagulation at INR 2.0 to 3.0 for patients 75 years or older, or for younger patients with risk factors (prior thromboembolism, hypertension, diabetes, left ventricular ejection fraction less than 35 %, HF, thyrotoxicosis, persistent atrial thrombus on TEE, mitral stenosis, and prosthetic heart valve; higher INR targets may be indicated for this last risk factor). For patients younger than 75 years with no risk factors, aspirin at 325 mg per day is recommended. Anticoagulants at target INR 2.5 (range 2.0 to 3.0) are recommended for any patient with AF and stroke risk factors. The exact age threshold for anticoagulation among patients with no additional stroke risk factors other than AF is debated. The authors tend to favor anticoagulation starting at age 65 years among the minority of AF patients who have no other risk factors for stroke. These recommendations apply to patients with intermittent (paroxysmal) or sustained AF.

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