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STROKE EVENT RATES AND THE OPTIMAL ANTITHROMBOTIC CHOICE OF PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract:

Although the stroke rate associated with atrial fibrillation has declined over the last 10 years, the emerging atrial fibrillation epidemic threatens to increase the incidence of cardioembolic stroke.

Oral anticoagulants are superior antithrombotic agents but are underused due to fear of bleeding and uncertainty about which patients will benefit. Individualized decisions on antithrombotic therapy require balancing the competing risks of thromboembolism and bleeding. The CHADS2 (Congestive heart failure, Hypertension, Age 75 years, and Diabetes mellitus, and 2 points for prior Stroke/transient ischemic attack) score and other schemes provide an estimate of thromboembolic risk; however, the external validity of these estimates in the context of well-controlled risk factors, or a hypercoagulable state, is uncertain. Moreover, it is very difficult to estimate bleeding risk. Recent studies highlight the need for meticulous international normalized ratio control to achieve optimal outcomes hampered by the high bleeding risk during oral anticoagulant inception and other limitations of warfarin. Dabigatran is at least as efficacious as warfarin in preventing stroke and systemic embolism for patients in whom the risk of thromboembolism outweighs bleeding risk. In addition, the results of ongoing trials evaluating alternative anticoagulants such as oral anti-Xa agents are awaited.

In this study, we discuss emerging therapies including available and completed trials of direct antithrombins and anti-Xa agents, including ximelagatran, idraparinaux, and dabigatran; and new device therapies including left atrial appendage occlusion devices. In light of these promising new therapies, it is likely that atrial fibrillation thromboembolism guidelines will need to be rewritten and frequently updated

Keywords: *anticoagulation; atrial fibrillation; dabigatran; stroke prevention; warfarin*

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INTRODUCTION:

Atrial fibrillation (AF) is associated with twice the mortality of age-matched controls and 10-fold higher mortality within 4 months of diagnosis. In the last 25 years, the age- and sex-adjusted annual incidence of AF has increased by 12.6%.2 Although the incidence of stroke associated with AF has declined in the last 5 to 10 years, concurrent with increased oral anticoagulant (OAC) use and better blood pressure control, the rising incidence and increasing age of the population is projected to increase stroke burden from 38 million disability-affected life-years in 1990 to 60 million disability-affected life-years by 2020. The past year has seen the publication of results of some of the largest and arguably most significant clinical trials of antithrombotic and other strategies to prevent stroke among patients with AF. In this review, we discuss these results in the context of current best evidence and examine how they may impact on the prophylactic antithrombotic management of patients with AF.

Thrombus Formation in AF

AF results in a loss of organized atrial contraction and is associated with stasis in the left atrial appendage (LAA), reduced LAA flow velocities, and thrombus formation. When AF is of □2 days' duration, atrial thrombi may be seen in up to 14% patients on transesophageal echocardiography ranging from 0.2 to 4.2 cm in size.6 Embolic strokes caused by AF are typically larger, more commonly disabling and fatal, and occur at more advanced age compared with strokes occurring in sinus rhythm. However, up to 25% of AF associated strokes originate from alternate sources, including the left ventricle, aortic arch, extracranial arteries, and in situ disease of the intracranial cerebral arteries.

Patients with AF and rheumatic mitral valve disease have a high risk of stroke, and OACs are indicated. In non-valvular AF, the annual stroke risk on aspirin is similar for paroxysmal (3.2%) and permanent (3.3%) AF, so recommendations on antithrombotic therapy pertain equally to both. The stroke risk with atrial flutter is intermediate between sinus rhythm and AF; however, up to 75% have coexistent AF or later develop it. Therefore, guideline recommendations are similar. For patients with lone AF (60 years without risk factors or structural heart disease), the cumulative risk of stroke over 15 years is very low (approximately 1.3%). In patients with non-valvular AF, the strongest independent predictor of stroke is prior stroke/transient ischemic attack (relative risk [RR], 1.9 to 3.7), increasing the annual stroke risk to 12%/year with no antithrombotic therapy and 10%/ year on aspirin. Age increases the relative risk of stroke/ systemic embolism by 1.4 with each decade. Other independent risk factors include hypertension, diabetes mellitus (RR, 1.7), and recent cardiac failure or moderate–severely impaired left ventricular ejection fraction (RR, 1.4).

The CHADS2 Index is a widely used risk scheme in AF, allocating 1 point for each risk factor of Congestive heart failure, Hypertension, Age 75 years, and Diabetes mellitus, and 2 points for prior Stroke/transient ischemic attack (Table 1).

Table 1. Annual Risk of Stroke With Nonvalvular AF Not Treated With Anticoagulation (With 95% CIs) According to the $CHADS_2$ Score*[18,19]

$CHADS_2$ Score	Stroke Risk (%)	95% CI	Patients (n=1733)
0	1.9	1.2–3.0	120
1	2.8	2.0–3.8	463
2	4.0	3.1–5.1	523
3	5.9	4.6–7.3	337
4	8.5	6.3–11.1	220
5	12.5	8.2–17.5	65
6	18.2	10.5–27.4	5

*The adjusted annual stroke rate was derived from multivariate analysis assuming no aspirin use.

Based on risk factors, annual stroke risk on aspirin may be calculated to select patients who would benefit from OAC. The CHADS2 and other risk stratification schemes have only limited ability to accurately predict thromboembolism in patients with AF20 A comparison of 5 risk stratification schemes to predict thromboembolism in a large community-based cohort of 13 559 adults with AF revealed that the risk schemes had only fair discriminating ability with C-statistics ranging from 0.56 to 0.62 (0.58 for the CHADS2 score; Table 2)

Table 2. Three Common Schemes of Stratifying Risk of Stroke Among Patients in AF[21]

$CHADS_2$	ACC/AHA/ESC Guideline	ACCP Practice Guidelines
Congestive heart failure—1 point*	High risk Prior thromboembolism†	High risk Prior thromboembolism†
Hypertension—1 point‡	≥2 moderate risk features	≥2 moderate risk features
Age >75 years—1 point		
Diabetes—1 point	Moderate risk	Intermediate risk
Stroke/TIA—2 points	Age ≥75 years	Age ≥75 years
	Heart failure§	Heart failure§
Low risk: 0 points	Hypertension‡	History of hypertension ‡
Moderate risk: 1 point‖	Diabetes	Diabetes
High risk: ≥2 points	Left ventricular ejection fraction <35% or fractional shortening <25%	Moderately to severely impaired left ventricular systolic function¶
	Low risk**	Low risk**
	No moderate- or high-risk features	No intermediate or high-risk features

These risk stratification schemes provide an estimate of risk and do not take into account the severity and duration of risk factors. The stroke risk at 85 years is significantly higher than at 75 years, yet this is not taken into account in the CHADS calculation. Similarly, poorly controlled diabetes mellitus,

hypertension, and heart failure probably pose an increased risk relative to well-controlled disease. Large left atrial size and spontaneous echo contrast are also omitted. It is uncertain whether scores like CHADS remain externally valid now with better risk factor control; it is noteworthy that in recent trials, stroke risk for CHADS has diminished. Clinical features that would favor OAC use over aspirin include moderate–severe left ventricular dysfunction, LAA thrombus/spontaneous echo contrast, reduced velocities within the LAA, and aortic atheroma on transesophageal echocardiogram.

Assessing Risk of Bleeding With OAC:

In clinical studies with careful monitoring of anticoagulant intensity, treatment with OAC increases the risk of major bleeding by 0.3 to 0.5%/year, from approximately 1%/year to 1.4%/year, and the risk of intracranial hemorrhage by 0.2%/ year compared with patients without OAC. However, higher (but variable) rates have been reported in patients on OAC in clinical routine practice. “Real-life” patients are older with less well-regulated anticoagulation therapy, and the average annual rate of major hemorrhage is 1% to 5% varying with intensity of anticoagulation and age. Major risk factors for bleeding with OAC include a concomitant bleeding tendency (eg, recent hemorrhage, uncontrolled anticoagulation, liver and kidney disease, the concomitant use of aspirin and nonsteroidal anti-inflammatory drugs), uncontrolled hypertension, binge drinking, ethnicity/race, and increasing age.

Chronic renal disease results in substantial changes in hemostasis with the paradox that patients in all stages of chronic renal disease, but especially with end-stage renal disease, have both a prothrombotic state predisposing to high risk for thromboembolism and coagulopathy with an increased tendency for bleeding. Although oral anticoagulation is the treatment of choice for AF, its use in patients with chronic renal disease is reported only in limited studies, all in patients on hemodialysis, and is associated with a markedly increased rate of bleeding compared with patients without chronic kidney disease.

Emerging Pharmacologic Therapies:

Direct Thrombin Inhibitors:

The direct thrombin inhibitor ximelagatran was 1 of the first oral anticoagulants to be evaluated as a potential warfarin alternative but was later withdrawn due to rare and potentially fatal hepatotoxicity. The Atrial fibrillation trial of Monitored, Adjusted Dose vitamin K antagonist, comparing Efficacy and safety with Unadjusted SanOrg 34006/idraparinux (AMADEUS) trial comparing idraparinux (subcutaneously injected factor Xa inhibitor) with warfarin was stopped early due to excess bleeding. Dabigatran is a congener of ximelagatran without hepatotoxicity, which has undergone extensive trialing.

It also requires no anticoagulant monitoring and has few interactions but requires twice-a-day dosage and effects cannot be acutely reversed with certainty. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) study, a total of 18 113 patients with nonvalvular AF and at least 1 risk factor for stroke were randomized to low-dose (110 mg twice daily) or high-dose dabigatran (150 mg twice daily) or to adjusted-dose warfarin (INR, 2 to 3). After a median follow-up of 2.0 years, the rates of the primary outcome, systemic embolism, or stroke (including hemorrhagic stroke) were similar among patients assigned 110 mg dabigatran twice daily and warfarin (RR, 0.91; 95% CI, 0.74 to 1.11; P0.001 for noninferiority) and significantly lower among patients assigned 150 mg dabigatran twice daily (RR, 0.66; 95% CI, 0.53 to 0.82; P0.001 for superiority).

Table 3. Current Trials of Anticoagulant Treatments in the Prevention of Stroke in Patients With AF[42]

	Design	Study Size, No.	Patients	Interventions	Outcome	Results Expected
ROCKET-AF	Randomized, double-blind, double-dummy, noninferiority	14 266	AF plus ≥2 risk factors for stroke	Rivaroxaban 20 mg daily plus warfarin placebo versus warfarin (INR, 2.0 to 3.0) plus rivaroxaban placebo	Stroke or noncentral nervous system embolism; clinically relevant bleeding	2010
ARISTOTLE	Randomized, double-blind, double-dummy, noninferiority	15 000	AF plus ≥1 risk factor for stroke	Apixaban 5 mg twice a day plus warfarin placebo versus warfarin (INR, 2.0 to 3.0) plus apixaban placebo	Stroke or noncentral nervous system embolism; clinically relevant bleeding	2010
AVERROES	Randomized, double-blind, superiority	5600	AF plus ≥1 risk factor for stroke, 40% warfarin naive	Apixaban 5 mg twice a day versus aspirin	Stroke or noncentral nervous system embolism; clinically relevant bleeding	Stopped early for efficacy June 2010
ENGAGE-AF TIMI-48	Randomized, double-blind, double-dummy, noninferiority	16 500	AF plus ≥1 risk factor for stroke	Edoxaban plus warfarin placebo versus warfarin (INR, 2.0 to 3.0) plus edoxaban placebo	Stroke or noncentral nervous system embolism; clinically relevant bleeding	2012
AZD0837 Trial	Randomized, parallel-group, dose-guiding study	250	AF plus ≥1 risk factor for stroke	AZD0837 150 mg twice a day or AZD0837 350 mg twice a day versus warfarin (INR, 2.0 to 3.0)	Stroke or noncentral nervous system embolism; clinically relevant bleeding	2010

OAC in the Elderly:

Elderly patients show a greatly increased major hemorrhage risk during OAC inception, especially if 80 years or CHADS 3.34 The annual risk of major bleeding in patients 80 years who are not enrolled in clinical trials approximates 2%.53 Elderly patients with AF derive greater benefit from OAC at the expense of increased major hemorrhage. Aiming for an INR at the lower end of the therapeutic range (2.0 to 2.5) may be a reasonable benefit/risk tradeoff for primary prevention in elderly patients with non-valvular AF. The results from Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) and other small randomized studies indicate that highly select, low-risk very elderly patients do benefit from OAC use, but these results may not be generalizable due to high rates of aspirin/OAC use before trial enrollment in BAFTA. In the absence of clear evidence, the pragmatic approach would be to prescribe aspirin or possibly low-dose dabigatran in the very elderly with a frank discussion about safety/efficacy tradeoff.

Other Therapeutic Strategies to Reduce Stroke in AF:

A rhythm over rate control strategy has not been shown to reduce the risk of stroke in atrial fibrillation. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, ischemic stroke rate was 1%/year in both rate and rhythm control groups with most strokes occurring in patients whose warfarin was stopped or subtherapeutic. In a post hoc analysis of A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter (ATHENA), the antiarrhythmic dronedarone was associated with less AF and reduced risk of stroke. Dronedarone also modestly reduced blood pressure and may have contributed to stroke prevention by either of these mechanisms. Dronedarone should not as yet be prescribed for stroke risk reduction until these mechanisms have been further clarified or additional studies confirm the observations.

CONCLUSION:

The current therapeutic challenge of adequately managing the burden of AF in the community is currently not met. There is a strong therapeutic need for alternative anticoagulants to OACs and a number of once or twice daily, orally administered drugs with no requirement for coagulation monitoring and dose titration are under development and in Phase III trials. After the disappointment with efficacy of dual antiplatelet therapy, and liver toxicity with ximelagatran, dabigatran was the first of these new drugs to be reported. It is important that the positive results with this drug, which may change practice, not derail the large ongoing trials of alternative anticoagulants, including oral anti-Xa and other drugs. It is hoped that other agents with equivalent or superior efficacy and safety to OAC, but without

OAC inconveniences, will ultimately improve patient compliance and narrow the AF treatment gap.

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