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STATE-OF-THE-ART PAPER

Left Atrial Appendage Occlusion

Opportunities and Challenges

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Stroke prevention in patients with atrial fibrillation is a growing clinical dilemma as the incidence of the arrhythmia increases and risk profiles worsen. Strategies in patients with nonvalvular atrial fibrillation have included anticoagulation with a variety of drugs. Knowledge that stroke in this setting typically results from thrombus in the left atrial appendage has led to the development of mechanical approaches, both catheter-based and surgical, to occlude that structure. Such a device, if it were safe and effective, might avoid the need for anticoagulation and prevent stroke in the large number of patients who are currently not treated with anticoagulants. Regulatory approval has been difficult due to trial design challenges, balance of the risk-benefit ratio, specific patient populations studied, selection of treatment in the control group, and specific endpoints and statistical analyses selected. Accumulating data from randomized trials and registries with longer-term follow-up continues to support a role for left atrial appendage exclusion from the central circulation as an alternative to anticoagulation in carefully-selected patient populations. (J Am Coll Cardiol 2014;63:291–8) © 2014 by the American College of Cardiology Foundation

By virtue of its increasing incidence and the increased potential for embolic stroke, atrial fibrillation (AF) is among the most complex and difficult challenges in the field of modern cardiovascular disease, and it represents a major health concern (1–5). The projected number of patients in the United States will be approximately 10 million by 2050 (3). In the setting of nonvalvular AF, two-thirds of strokes are cardioembolic. Echocardiographic and pathologic studies suggest that when a source can be identified, approximately 90% of such strokes can be attributed to thrombus in the left atrial appendage (LAA) (6).

The relationship between the increased burden of AF with advancing age and the increased incidence of related stroke has been well described (1,2,5). This is a cause for concern because of the attendant increased mortality and morbidity from AF-related stroke; cardioembolic strokes are particularly catastrophic, resulting in the worst prognosis among the various causes of stroke (1,7–9). The search for strategies to prevent or at least decrease stroke frequency in this setting has drawn considerable attention; this review provides an overview of these strategies with a focus on nonpharmacological approaches.

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Risk Prediction Models

Prediction of stroke. Models for prediction of stroke risk most commonly have relied on clinical variables (10–14). Evaluation and comparison of multiple models have documented relatively poor performance, with inability to predict central nervous system events. In a study of 79,884 patients followed for an average of 4 years, risk prediction models were found to have only modest discriminatory ability, with C-statistics of approximately 0.60 (12). The most commonly used model has been $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack) score (Table 1), although this has now been largely supplanted by the CHA_2DS_2 VASC ($CHADS_2$ plus vascular disease, age 65 to 74 years, and female sex) score (Table 1), which has the advantage of discriminating the potential for stroke in lower-risk patient groups, and thereby might facilitate the selection of preventive strategies that are more specific (11,12).

Prediction of bleeding risk. A variety of bleeding risk scores have also been developed. Recently, 3 scoring systems

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
INR = international normalized ratio(s)
LAA = left atrial appendage
NOAC = novel oral anticoagulant
RR = rate ratio

have been evaluated in patients with AF (15). These included ATRIA (anticoagulation and risk factors in AF), HEMORR$_2$HAGES (hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, and stroke), and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or pre-disposition, labile international normalized ratio [INR], >65 years, drug or alcohol use) (15). The latter score has become perhaps the most widely used. When applied in 2,293 patients with AF who were randomized to either fixed-dose Idraparinux (sanofi-aventis, Bridgewater, New Jersey) or adjustable-dose oral vitamin K, the HAS-BLED score performed best in predicting any clinically-relevant bleeding. In addition, the HAS-BLED score was the only one that demonstrated significant prediction for intracranial hemorrhage. However, all 3 scores demonstrated only modest performance in predicting any clinically-relevant bleeding, with C-indexes below 0.70 (15).

Anticoagulant therapy. Anticoagulant therapy has been the mainstay of therapy for stroke prevention in AF (1,16–24). Limited initially to warfarin, several important observations and conclusions have been drawn. Although warfarin therapy is very effective in reducing ischemic stroke (in contrast to acetylsalicylic acid, which has very limited effectiveness), several issues with it have been identified (1,24–31):

1. Less than 50% of patients at risk for stroke are prescribed or fill a prescription for warfarin on presentation with AF. This relates to several factors, including patient preference and real or perceived relative or absolute contraindications that are typically related to concerns for bleeding hazard (9,28–30).
2. Of those patients prescribed warfarin, there is ongoing attrition of its use to approximately 40% by 4 years (31).
3. During periods where warfarin must be withheld, such as for surgery or significant bleeding, patients are exposed to a window of thromboembolic risk.
4. Variable control of INR is frequent, with only approximately 60% of serial INR in randomized clinical trials being within therapeutic range (24–27,32).
5. There is patient inconvenience and cost with long-term monitoring of INR, dose adjustments, and multiple drug-to-drug interactions.
6. The risk of bleeding is increased when warfarin is administered along with dual antiplatelet therapy for associated conditions such as drug-eluting stents (33–35). When bleeding occurs in this setting, both warfarin and the dual antiplatelet therapy may be withheld, increasing the risk of stent thrombosis.

Table 1 $CHADS_2$ Scores

$CHADS_2$ Score		CHA_2DS_2 VASC Score	
Risk Factor	Score	Risk Factor	Score
CHF	1	CHF/LF dysfunction	1
Hypertension	1	Hypertension	1
Age ≥75 yrs	1	≥75 yrs	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA	2	Stroke/TIA	2
		Vascular disease	1
		65–74 yrs	1
		Female sex	1

Two commonly used scores for risk prediction of stroke in patients with nonvalvular atrial fibrillation. With these scores, there is an increase in the incidence of stroke with an increasing additive score.

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack; CHA_2DS_2 VASC = $CHADS_2$ plus vascular disease, age 65 to 74 years, and female sex; CHF = congestive heart failure; LF = labile factor; TIA = transient ischemic attack.

Because of these issues, novel oral anticoagulants (NOACs) have been developed and tested in large-scale randomized clinical trials in aggregate enrolling >50,000 patients (36–43) (Table 2). Although most studies with NOACs have shown them to be either noninferior or superior to warfarin for stroke reduction, bleeding rates have been somewhat variable. Compared with warfarin, both factor Xa inhibitors and 2 doses of the direct thrombin inhibitor dabigatran showed a large reduction in hemorrhagic strokes (36–44). Major bleeding rates with these agents, however, still exceeded 2% to 3% per year, and minor bleeding rates were over 10% per year (36). Thus, although improved, hemorrhagic complications remain a significant and serious limitation of new oral anticoagulants. When major bleeding occurs, it is associated with increased risk of death that, although less than with warfarin, is still substantial. As previously mentioned, a major complication with bleeding is that it often leads to discontinuation of antithrombotic therapy at least until the bleeding risk is minimized, leaving the patient exposed to the underlying thromboembolic risk. Consequently, within 2 years of initiating therapy with NOACs, approximately 20% of patients have discontinued them (36). One advantage of the NOACs is that they do not require monitoring, which makes them more clinically acceptable than warfarin, but this paradoxically limits the physician's ability to ensure patient compliance, particularly with the short half-lives of these NOACs. Furthermore, the lack of widely available antagonists renders management problematic when emergency surgical procedures are necessary or when bleeding occurs.

There are no direct head-to-head trials comparing the NOACs. A recent meta-analysis (40) included 44,733 patients from 4 studies that included apixaban, dabigatran, and rivaroxaban versus warfarin. Using adjusted indirect comparisons, there was significant heterogeneity in results. Dabigatran lowered the composite of systemic emboli or

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