New Therapies for Stroke Prevention in Atrial Fibrillation
The Long Road to Enhanced Efficacy

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Atrial fibrillation is the most frequent sustained arrhythmia seen in clinical practice, and the public health implications of this growing epidemic are sobering. Approximately 2.3 to 3.2 million people are currently affected in the United States; the risk of stroke ranges from 1% to 7% per year; and atrial fibrillation accounts for \(\approx 45\%\) of embolic strokes annually, which amounts to \(\approx 100,000\) strokes per year.\(^1\)\(^2\) Moreover, atrial fibrillation is an independent predictor of mortality in most studies.\(^3\)

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Atrial fibrillation is a frequent cause for hospitalization, and during the last 2 decades, hospitalization rates for atrial fibrillation as the principal diagnosis have increased substantially.\(^4\)\(^5\) The economic consequences of this disorder are substantial.\(^6\) In the United Kingdom, the cost of hospitalizations for atrial fibrillation increased 123% between 1995 and 2000\(^7\) and in 1995 accounted for 0.62% of the entire budget of the National Health Service.

Future projections are even more disturbing. The prevalence of atrial fibrillation increases with age, and the demographic tide around the world is resulting in increasingly aging societies. Moreover, the age-adjusted incidence and prevalence of atrial fibrillation in Olmsted County have increased significantly between 1980 and 2000, and on the basis of these projections, the number of persons with atrial fibrillation could exceed 12 million by 2050.\(^1\) It is estimated that 35% of the increased prevalence is due to an increased incidence, 43% to the result of greater longevity, and 22% to a growing census. In summary, atrial fibrillation is a costly disease from both a clinical and economic perspective, and the burden is increasing. There is a dire need for new therapies and preventive approaches.

In atrial fibrillation, the primary therapeutic objectives are to prevent stroke and to improve symptoms, whether by controlling the ventricular response rate or restoring and maintaining sinus rhythm. Although the objectives are clear, the clinical management is often challenging and nuanced, a reflection in part of the wide diversity of patient demographic and clinical variables and individual tolerance of the arrhythmia.

Several clinical trials have demonstrated that the strategy of rate versus rhythm control results in similar outcomes, particularly among the elderly with risk factors for stroke.\(^8\)\(^9\) It should be emphasized, however, that patients entered in these trials were, by design, selected on basis of their tolerance of symptoms to allow randomization. Highly symptomatic patients and patients with reduced left ventricular compliance caused by left ventricular hypertrophy, diastolic heart failure, and hypertrophic cardiomyopathy were underrepresented. Nonetheless, subset analyses suggest that the maintenance of sinus rhythm may be beneficial for some patients, although the extent to which sinus rhythm is a surrogate as opposed to a cause-and-effect relationship is uncertain.\(^10\) Major limitations of the strategy of rhythm control, however, are the relative inefficiency and toxicity of currently available antiarrhythmic drugs and the lack of long-term outcome data in regard to nonpharmacological approaches such as radiofrequency pulmonary vein and circumferential left atrial ablation.

From the perspective of the patient, embolic stroke is the most catastrophic complication of atrial fibrillation, and its prevention is one of the most challenging but dynamic areas of atrial fibrillation investigation. The mechanisms of thromboembolism are multifactorial, and although stasis and thrombosis in the left atrial appendage are likely the most frequent underlying causes, preexisting atherosclerotic vascular disease may play an important role.\(^11\) The risk of stroke varies widely, depending on the presence or lack thereof of risk factors such as prior thromboembolism, hypertension, advanced age, diabetes, congestive heart failure, and valvular heart disease.\(^12\) Although the CHADS2 (congestive heart failure, hypertension, age, diabetes, stroke) score is clinically useful in determining the risk of stroke, the clinical decision to initiate anticoagulant therapy requires an equally critical assessment of the risk of bleeding and compliance. Paradoxically, patients who may benefit the most from anticoagulant therapy to prevent stroke may also be at the highest risk of bleeding. What complicates the decision further is the frequency of “clinically silent” recurrences of atrial fibrillation in patients who are in apparent sinus rhythm after antiarrhythmic drug therapy or radiofrequency ablation. In the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial of rate versus rhythm control, stroke occurred in both groups, particularly in patients among whom anticoagulants were discontinued on the assumption that sinus rhythm was successfully maintained.\(^9\) In these patient subsets, we know very little about the burden of atrial fibrillation in regard to the impact of the frequency and duration on
thromboembolic risk and the need for continued anticoagulation. This is a focus of current investigation, but answers will not be easily forthcoming.

For the prevention of stroke risk in atrial fibrillation, warfarin is the sole oral anticoagulant currently used in the United States and has been commercially available for >50 years. With an estimated 2 million people initiating warfarin therapy each year, the efficacy and safety of warfarin and related oral anticoagulants are central issues in stroke prevention. Much has been written about the disadvantages of warfarin and other vitamin K antagonists. The therapeutic window for stroke prevention versus hemorrhage is narrow; dosage may be unpredictable because of genetic and extrinsic factors such as drug and food interactions; and international normalized ratio monitoring is inconvenient. It is widely accepted that the development of anticoagulation agents that are free of the limitations of warfarin would fill an unmet need, but this is a challenging objective because warfarin, for all of its faults, works remarkably well.

These well-characterized risks of venous thromboembolic treatment and the growing rate of atrial fibrillation/thrombosis have spurred the development of new therapeutic agents. In the area of venous thromboembolism, drugs are being developed that target the specific steps of coagulation, including initiation, propagation, and thrombin activity. Initiation of coagulation is inhibited primarily by agents that target the factor VIIa/tissue factor complex, although many of the therapies being developed in this class are intravenous/subcutaneous and are not considered long-term options for stroke prevention in atrial fibrillation. Drugs being developed to block the phase of coagulation propagation target factor IXa and factor Xa or inactivate factors Va and VIIIa. As with the inhibitors of initiation, many of the indirect factor Xa and VA inhibitors are subcutaneous/intravenous. However, many of the direct factor Xa inhibitors are given orally, and some such as apixaban and rivaroxaban are in later stages of evaluation. Finally, thrombin inhibitors prevent fibrin formation and block thrombin-mediated activation of other coagulation factors. In this issue of Circulation, Ellis and colleagues study a new anticoagulant in patients with atrial fibrillation. Interestingly, rather than targeting the coagulation cascade in a directed manner, this study examines the effect of tecarfarin (ATI-5923), another oral vitamin K antagonist. Tectarfarin is a vitamin K epoxide reductase antagonist that is stated to have mechanisms of action identical to those of warfarin. The advantage of tecarfarin over warfarin is that it is metabolized by carboxylesterases and not the cytochrome P450 (CYP450) pathway. This difference could potentially decrease many of the drug, food, and genetic interactions resulting from the CYP450 system. Specifically, variants in the CYP450 2C9 gene are associated with impaired warfarin metabolism and have been reported to account for ≈10% of the dose variance. If some this variability is avoided, the ability to achieve and maintain a therapeutically normalized ratio could be increased. Importantly, the most vulnerable period for warfarin-induced adverse events occurs during initiation, with the first 3 months associated with a 3-fold increased risk of major bleeding. By targeting the early dosing variability, it is possible that tecarfarin could minimize the side effects occurring as a result of overdosing and underdosing, particularly in older patients.

Conclusions that can be drawn from the study by Ellis et al are limited because it was an open-label study of limited size. The primary outcome was time in therapeutic range. Compared with past warfarin studies, this was an ≈10% improvement. However, because the duration of study was also modest (6 to 12 weeks) and there was no warfarin control group, both long- and short-term comparisons with warfarin cannot be made. The study also assessed only patients of low to moderate risk for stroke. In the study, after 2 weeks of treatment with tecarfarin, 95% of the patients had attained a therapeutic international normalized ratio. Although there were many adverse events during the study, most were not related to the study drug, although there were the expected anticoagulant-related side effects of bruising, positive stool occult blood tests, and epistaxis. Only a much larger study can determine the true minor and major bleeding rates of this drug and its comparison with warfarin, both crucial pieces of information.

This study highlights more general concerns in regard to anticoagulant development for stroke prevention in atrial fibrillation. Although there is a consensus that better treatments for patients with atrial fibrillation at risk of stroke are needed, there are a number of complex issues in regard to the design of randomized controlled trials that should be addressed. Newer antithrombotic therapies need to be compared with warfarin because placebo-controlled trials in most patients with atrial fibrillation are not feasible from an ethical standpoint. This would not apply, however, to trials in which a new agent is compared with placebo or aspirin in a patient population considered unsuitable for warfarin therapy because of a perceived risk of bleeding or compliance, for example.

The selection of appropriate end points is also crucial in the clinical study of new anticoagulants under development. Stroke and systemic embolism have been the primary end points in many prior trials, but other outcomes that are common in older patients with atrial fibrillation are major bleeding, myocardial infarction, and death, all of which could be affected by various antithrombotic strategies. As highlighted by the study by Ellis and colleagues, approaches to account for “softer” but nonetheless clinically relevant end points such as convenience, frequency, international normalized ratio monitoring, and drug interactions need to be developed.

In placebo-controlled trials in patients who are not candidates for warfarin, a superiority trial design is feasible. The majority of trials of a new agent, however, will be active comparator trials versus warfarin, and the low event rates will require large numbers of patients and a noninferiority design. Establishing the credible boundaries for noninferiority that will also satisfy regulatory issues is a difficult and crucial issue. Other issues to be taken into account and that enhance the complexities of trial design include an open-label trial as opposed to blinding, the inclusion of a substantial proportion of warfarin-naïve patients (because the lability of warfarin is greatest during the early period after the initiation of therapy),...
the incorporation of utility-based metrics, and measures of cost-effectiveness. Indexes of patient-related convenience and discomfort are highly relevant to the development of new therapies but with a caveat that these potential advantages will not overcome clinical effectiveness on primary end points such as major stroke.

In summary, the growing burden of atrial fibrillation, the most frequent sustained arrhythmia seen in clinical practice, is staggering. As highlighted by the present study by Ellis and colleagues, identifying new treatments is crucial in the management of this expanding problem and has the potential to mitigate some of the public health implications. Warfarin, despite its many challenges and limitations, has been carefully and extensively studied and is used widely and successfully; thus, any new therapy will have to establish efficacy, safety, and cost-effectiveness using logical and relevant trial design. Clearly, a therapy that removes many of the burdens of warfarin therapy would be greatly welcomed, but for this to become a clinical reality requires careful steps down a long and difficult road.

Disclosures

None.

References

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