Managing thromboembolic risk in patients with atrial fibrillation: are we approaching a new frontier?

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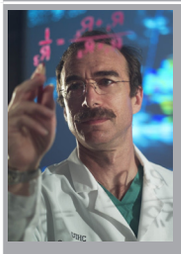

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The risk of thromboembolic events, particularly stroke, is increased in patients with atrial fibrillation. Therefore, it is vitally important to identify effective strategies for adequate anticoagulation, especially for those at greatest risk. Determining which patient has a substantial risk and is most likely to derive benefit from anticoagulation without incurring excessive bleeding risk, however, is far from simple. The exact mechanisms and patient characteristics lending to this increased risk of thromboembolism in atrial fibrillation are still being defined. Furthermore, current anticoagulation strategies are often cumbersome in clinical practice, replete with risks and restrictions, do not fully negate the risk of thromboembolism and, as such, are unpalatable to patients and physicians alike. Several newer anticoagulants, including factor Xa antagonists and direct thrombin inhibitors, appear promising despite the underlying complexities of atrial fibrillation. Recent data concerning dabigatran [1], a direct thrombin inhibitor, are compelling and give us pause to consider whether we are approaching a new frontier in the management of thromboembolic risk in atrial fibrillation patients.

There are several described mechanisms responsible for the increased risk of thromboembolic events in patients with atrial fibrillation [2]. One simple explanation is that inadequate atrial emptying, due to the rhythm itself, can cause stagnation of blood and a greater propensity for thromboembolic events. Similarly, atrial remodeling as a result of fibrillation may increase the risk. Still, another consideration is that atrial fibrillation may lead to the activation of procoagulant pathways, perhaps based on an inflammatory response. Thromboemboli may also originate from noncardiac sources [3]. Despite these and other possible explanations, ongoing research seeks to better understand and characterize the responsible mechanisms so that treatment options may be developed to target these pathways.

Comorbidities increase the risk of thromboembolism in atrial fibrillation patients. Various scores that consider specific nonmodifiable clinical characteristics have been developed to identify patients with nonvalvular disease at significant risk – the greater number of risk factors, the greater risk of stroke and need for anticoagulation.

The $CHADS_2$ score, which assigns one point to the presence of congestive heart failure, hypertension, age older than 75 years or diabetes, and two points to a history of stroke or transient ischemic attack, is commonly used to stratify the risk of thromboembolism in patients with nonvalvular atrial fibrillation. A score of 2 places a patient at an annual stroke risk of 4.0%; the annual risk of stroke is as high as 18.2% for those with a score of 6 [4–6]. While the annual risk of bleeding also varies by $CHADS_2$ score [7], benefit in favor of warfarin anticoagulation increases when the score exceeds 1. The score, however, underestimates the substantial risk of thromboembolism in some patients with atrial fibrillation. As a result, a more sophisticated and inclusive score, CHA_2DS_2-VASc, incorporates female gender, age of 65–74 years and presence of vascular disease as additional risk factors, each with its own impact [8].

Unfortunately, little attention is directed towards the paroxysmal and intermittent nature of atrial fibrillation in these risk stratification schemes. Patients may not be considered for anticoagulation after a documented return to sinus rhythm even though recurrent, but asymptomatic and occult atrial fibrillation puts patients at continued risk. In reality, any episode of atrial fibrillation has associated thromboembolic risk, although the risk may be acceptably low. The use of an anticoagulant, like warfarin, involves evaluating this risk and balancing it against the risk of bleeding [9], adverse effects and complexities of administration.

The aforementioned risk stratification scores aid in determining which patients with atrial

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fibrillation may benefit from warfarin anticoagulation as, until now, no other pharmacologic strategy has proven as efficacious in randomized controlled clinical trials. Aspirin, arguably effective in a select population [10,11], may work by other mechanisms, such as prevention of thromboembolism from carotid or aortic disease. Even clopidogrel and aspirin combinations, while more effective than aspirin alone, do not appear to be as efficacious as warfarin [12].

Anticoagulation with warfarin is complex. For warfarin to be effective, routinely monitored international normalized ratio (INR) values must remain within a narrow therapeutic range (INR: 2.0–3.0) at least 65% of the time [13]. Despite frequent dose adjustments, this is often not the case [14]. Patient compliance with diet and drug regimens is required to achieve consistent anticoagulation; yet, sometimes wide and unexplained INR fluctuations occur, making warfarin use untenable. Warfarin anticoagulation is not immediate and there is the possibility of increasing the thromboembolic risk with drug initiation due to transient deficiencies of proteins C and S. Bridging anticoagulant therapy with heparin, until a therapeutic INR is achieved, may be necessary. Even then, such adjunctive therapy is not proven beneficial in light of its additional risks.

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Warfarin anticoagulation introduces inherent risks of bleeding. Prompt reversibility of anticoagulation is not always possible. Owing to concerns of bleeding, patients may opt not to take warfarin; likewise, physicians may choose not to prescribe it. Ultimately, these decisions affect 50% of the entire atrial fibrillation population at high risk for stroke [15–18], although the actual number of people who could benefit, but do not take warfarin, remains in dispute [19,20]. Warfarin nonadherence and patient misinformation concerning anticoagulation are major issues [21,22]. Often, patient and physician concerns are incongruent [23,24]. These patients, mostly the elderly, remain at continued risk for thromboembolism.

The potential advantages of an anticoagulant superior to warfarin are clear. On the other hand, warfarin effectively reduces the risk of stroke in atrial fibrillation patients, is inexpensive, and is the 'gold standard' by which other anticoagulants are judged. Thus, it is difficult to justify looking for an alternative. Studies seeking to find a new therapeutic option have required a noninferiority design, and have considered complications and risks, as well as the benefits, in determining drug superiority. The efficacies of ximelagatran [25,26] and idraparinux [27] may be similar to warfarin but at an additional price. Associated liver toxicity and excess bleeding risk, respectively, could not offset the potential benefit of these drugs.

Data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial have turned many heads and may ultimately change our approach to anticoagulation in patients with atrial fibrillation. The trial, conducted at 951 centers in 44 countries, randomized 18,113 patients with atrial fibrillation to receive either fixed low- (110 mg) or high- (150 mg) dose dabigatran twice daily or adjusted-dose warfarin [28]. The population included those with a mean age of 71 years and at least one other stroke risk factor. The mean $CHADS_2$ score for each group was 2, yet, nearly 32% of patients had a $CHADS_2$ score of 0–1. Aspirin use at baseline was 40% but the continual use of aspirin was nearly 20% throughout the study.

Over a median 2-year follow-up, the annualized rate of stroke or systemic embolism was 1.53% for low-dose dabigatran, 1.11% for high-dose dabigatran and 1.69% for warfarin. However, the annualized myocardial infarction rates trended higher in the dabigatran arms compared with warfarin (relative risk [RR]: 1.35; 95% CI: 0.98–1.87, p = 0.07 for low-dose dabigatran and RR: 1.38; 95% CI: 1–1.91, p = 0.05 for high-dose dabigatran). Annual major bleeding rates were 2.71% (p = 0.003 vs warfarin) for low-dose and 3.11% (p = not significant vs warfarin) for high-dose dabigatran; the rate was 3.36% for warfarin. Dyspepsia occurred more commonly with both doses of dabigatran compared with warfarin (p < 0.001).

This large, controlled, clinical trial demonstrated noninferiority of dabigatran at the 110 mg twice daily dose compared with warfarin, with reduced risk of serious bleeding, and superiority to warfarin at the 150 mg twice daily dose with no difference in serious bleeding risk. In fact, high-dose dabigatran reduced the annualized risk of stroke or peripheral embolic events by 34% (p < 0.001). Alternatively, while this RR seems impressive, the absolute difference between warfarin and dabigatran was only approximately 1% per year. Nevertheless, both doses were associated with fewer intracerebral bleeds.

The risk of noncardiac side effects was acceptably low; importantly, the risk of hepatotoxicity associated with ximelagatran, was not seen with dabigatran. Although promising, problems with the study include the open-label use of warfarin with the introduction of possible bias, as well as the relatively low incidence of myocardial infarction, heart failure and stroke or transient ischemic attack at baseline in the study population. These data may not apply to all atrial fibrillation patients at risk for thromboemboli.

> "*While we rely on warfarin to lessen the risk of thromboembolism today, if dabigatran survives the careful scrutiny of regulatory bodies and is approved, it will redefine the boundaries of the anticoagulation frontier tomorrow.*"

For the first time, a new anticoagulant, dabigatran, has demonstrated a benefit similar to warfarin in atrial fibrillation patients at risk for stroke. The advantages are manifold. Drug dosing is fixed with no need for titration or measurement of INR values, as is the case with warfarin administration. Anticoagulation with dabigatran is rapid, thereby eliminating the need for bridging with heparin or enoxaparin. Reversal of anticoagulation occurs upon termination of the medication. These properties of dabigatran make the drug potentially useful in patients requiring short-term anticoagulation, as in those with recent onset atrial fibrillation or in patients undergoing ablation. Patients who cannot maintain a therapeutic INR while on warfarin may gain benefit from anticoagulation with dabigatran. Patients and physicians who considered warfarin therapy tedious may find this drug attractive.

As with any new therapy, there are downsides to consider. Dabigatran may be unaffordable for many patients. Twice daily dosing may pose problems; however, patients may still benefit from dabigatran given the complexity, inconvenience and risks associated with warfarin. Safety and efficacy of dabigatran in a large number of patients with atrial fibrillation and risk for stroke who also require clopidogrel, aspirin or other antiplatelet drugs for coronary artery disease remain a concern. For this group, scrupulous testing is necessary to assess this drug combination. Patients taking warfarin, in whom the INRs remain stable, may prefer not to switch to dabigatran [29]. In a *post-hoc* and center-based analysis of the RE-LY trial, death, bleeding, stroke, systemic embolism and the composite were acceptably low when time in the therapeutic range with warfarin exceeded 65% [29]. In addition, dabigatran may have unique, but minor, side effects, such as dyspepsia, which must be considered. Thoughtful consideration by the clinician is required to make reasonable management recommendations for individual patients.

The market for dabigatran appears extremely large. Patients with atrial fibrillation and a high CHA_2DS_2-VASc score could benefit from a safe and effective anticoagulant. It is also likely that patients deemed to be at lower risk for stroke with atrial fibrillation, such as those with a $CHADS_2$ score of 0–1, could benefit from dabigatran. While catheter ablation techniques may, ultimately, cure atrial fibrillation, it remains uncertain whether the risk of thromboembolic events would be eliminated completely in those who have additional risk factors.

Ultimately, the RE-LY trial points toward the possibility that novel anticoagulation strategies with dabigatran can improve patients' lives. While we rely on warfarin to lessen the risk of thromboembolism today, if dabigatran survives the careful scrutiny of regulatory bodies and is approved, it will redefine the boundaries of the anticoagulation frontier tomorrow.

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