A New Era for Anticoagulation in Atrial Fibrillation

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For more than 50 years, warfarin has been the primary medication used to reduce the risk of thromboembolic events in patients with atrial fibrillation. Despite its clinical efficacy, warfarin has multiple, well-known limitations, including numerous interactions with other drugs and the need for regular blood monitoring and dose adjustments. Thus, clinicians and patients have been eager to embrace alternative oral anticoagulants that are equally efficacious but easier to administer.

In this issue of the Journal, Granger and colleagues report the impressive primary results of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE; ClinicalTrials.gov number, NCT00412984). A total of 18,201 subjects with atrial fibrillation and at least one additional risk factor for stroke were enrolled in the trial and were randomly assigned to receive the direct factor Xa inhibitor apixaban (at a dose of 5 mg twice daily) or warfarin (target international normalized ratio [INR], 2.0 to 3.0). The trial was designed to test whether apixaban was noninferior to warfarin with respect to efficacy. The investigators found that apixaban was not only noninferior to warfarin, but actually superior, reducing the risk of stroke or systemic embolism by 21% and the risk of major bleeding by 31%. In predefined hierarchical testing, apixaban, as compared with warfarin, also reduced the risk of death from any cause by 11%.

These results come on the heels of two other, large, phase 3 trials in which novel anticoagulants were compared with warfarin in patients with atrial fibrillation: the Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY, NCT00262600) and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF, NCT00403767). The RE-LY trial evaluated the direct thrombin inhibitor dabigatran in two different doses, 110 mg and 150 mg, both administered twice daily. ROCKET AF evaluated the direct factor Xa inhibitor rivaroxaban at a dose of 20 mg once daily.

The trials have a number of similar conclusions. Apixaban, dabigatran, and rivaroxaban, as compared with warfarin, all significantly reduce the risk of hemorrhagic stroke. In fact, in all the studies, the reductions in the primary efficacy end point — which included hemorrhagic as well as ischemic stroke — were greatly influenced by this dramatic reduction in the risk of hemorrhagic stroke. Of the three drugs, only dabigatran at a dose of 150 mg holds the distinction of also having significantly reduced the risk of ischemic stroke as compared with warfarin; nonetheless, even in this case, there was a greater influence on hemorrhagic stroke than on ischemic cerebrovascular events. Similarly, the risk of particularly serious bleeding was reduced with each of the three drugs, as compared with warfarin, and apixaban therapy also resulted in lower rates of all major bleeding. Thus, the newer anticoagulants boast favorable bleeding profiles as compared with warfarin in patients with atrial fibrillation.

There is also a shared theme with respect to mortality. Apixaban is the first of the newer anticoagulants to show a significant reduction in the risk of death from any cause as compared with warfarin (hazard ratio, 0.89; 95% confidence interval [CI], 0.80 to 0.99; P=0.047). Although the current findings are notable, both dabigatran and rivaroxaban, as compared with warfarin,
has been well controlled with warfarin for years. Sary for the individual patient in whom the INR switching to a newer agent may not be neces-
tary for the individual patient in whom the INR was observed with rivaroxaban in the intention-to-treat analysis in ROCKET AF (hazard ratio, 0.92; 95% CI, 0.82 to 1.03; P = 0.15). Thus, there is approximately a 10% reduction in the risk of death from any cause across these three trials in which the newer anticoagulants were compared with warfarin in patients with atrial fibrillation.

Despite these similarities, there are important differences in the design of the studies and in the administration of the drugs. In the RE-LY trial, the assignments to dabigatran or warfarin were not concealed. In contrast, the ROCKET AF and ARISTOTLE trials successfully achieved a double-blind design. In the RE-LY and ARISTOTLE trials, dabigatran and apixaban were administered twice daily; in ROCKET AF, rivaroxaban was administered once daily. Subjects in the RE-LY and ARISTOTLE trials could have only one additional risk factor for stroke, whereas ROCKET AF enrolled a higher-risk population. The mean percentage of time in which the INR was in the therapeutic range of 2.0 to 3.0 — a metric that assesses the quality of warfarin dosing — was 64% in the RE-LY trial, 55% in the ROCKET AF trial, and 62% in the ARISTOTLE trial. There were additional differences among the studies with respect to their statistical analysis plans and power. These factors highlight the challenges with cross-trial comparisons. Head-to-head studies, which are not currently available, would allow for direct assessments among these novel compounds.

Will these newer anticoagulants be better than warfarin for the treatment of all patients with atrial fibrillation? The direct thrombin and factor Xa inhibitors overcome the need for routine blood monitoring, and the trial results have been encouraging overall and across important subgroups. For example, in the ARISTOTLE trial, the efficacy of apixaban was consistent in subgroups according to baseline stroke risk and according to whether patients had or had not been taking warfarin before entering the study. However, switching to a newer agent may not be necessary for the individual patient in whom the INR has been well controlled with warfarin for years.

In addition, although the newer anticoagulants have a more rapid onset and termination of anticoagulant action than does warfarin, agents to reverse the effect of the drugs are still under development and are not routinely available.

In addition, generic warfarin is expected to be markedly less expensive than the newer agents even after the costs associated with regular INR monitoring are considered. One analysis has suggested that dabigatran, as compared with warfarin, could be cost-effective in patients with atrial fibrillation. Additional data on cost-effectiveness are likely to further influence clinical decision making. Thus, although the oral direct thrombin and factor Xa inhibitors are attractive alternatives, it is likely that warfarin will continue to be used worldwide in many patients with atrial fibrillation.

The original mission to replace warfarin began with a search for drugs that were simply noninferior to warfarin. The ARISTOTLE trial, in conjunction with the RE-LY and ROCKET AF trials, suggests that apixaban, dabigatran, and rivaroxaban have gone even further. Across three large studies with different populations of patients with atrial fibrillation, the direct thrombin and factor Xa inhibitors have been shown to have a more favorable bleeding profile than warfarin and are at least as efficacious. Information about another direct factor Xa inhibitor, edoxaban, in patients with atrial fibrillation, will be available at the conclusion of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction Study 48 (ENGAGE AF-TIMI 48, NCT00781391). After all this time, a new era of anticoagulation appears to be emerging for patients with atrial fibrillation.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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The Challenges of Intracranial Revascularization for Stroke Prevention

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The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial1 (SAMMPRIS, ClinicalTrials.gov number, NCT00576693), as reported by Chimowitz et al. in this issue of the Journal, showed that aggressive medical management alone was superior to intracranial arterial stenting with the use of the Wingspan stent system in addition to aggressive medical therapy in patients with a recent transient ischemic attack or stroke attributed to 70 to 99% stenosis of the diameter of a major intracranial artery. Three key lessons can be gleaned from the SAMMPRIS trial and previous trials of revascularization for stroke prevention: the challenges of intracranial revascularization are greater than those of revascularization of extracranial carotid stenoses; aggressive and attentive medical therapy is an effective approach to the prevention of stroke in high-risk populations; and the Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) play critical roles in the advancement of cost-effective medicine.

The SAMMPRIS trial is the third randomized trial of intracranial revascularization that has failed to show a benefit of that strategy over medical therapy for the prevention of stroke. Two trials of intracranial–extracranial bypass surgery for the prevention of stroke in patients with symptomatic internal carotid-artery occlusion — the Extracranial–Intracranial Bypass Trial2 and the Carotid Occlusion Surgery Study (COSS, NCT00029146)3 — were negative studies, which has led to very limited use of the bypass procedure. Although the bypass surgery in COSS accomplished the physiological goal of improving perfusion of blood to the brain, it was ineffective, as compared with medical therapy, in preventing recurrent stroke. Similarly, stenting in the SAMMPRIS trial decreased the stenosis of the symptomatic artery but was inferior to medical therapy in preventing recurrent stroke.

The 30-day rate of stroke or death associated with stenting in the SAMMPRIS trial (14.7%) is nearly 2.5 times as high as the 6% rate associated with stenting of symptomatic extracranial carotid-artery stenoses in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST, NCT00004732).5,5 One surprising finding was that symptomatic intracranial hemorrhage, a relatively rare complication after revascularization of extracranial carotid-artery stenosis,6 represented almost a third of all perioperative strokes in the SAMMPRIS trial. The intracranial hemorrhages were thought to be due to reperfusion hemorrhage or subarachnoid hemorrhage from wire manipulations during the procedure. This latter complication emphasizes the fact that stenting of the intracranial vasculature is technically more challenging than is stenting of the extracranial carotid artery because of the tortuous course of the internal carotid artery through bony canals, an abrupt right-angle turn for the middle cerebral artery, and arterial diameters that are smaller overall than those in the extracranial circulation. Small, penetrating brain arteries from the trunks of the middle cerebral and basilar arteries are often near or at the site of the placement of the stent and may be compromised. The circle of Willis can provide additional pathways for blood flow to the brain in patients with extracranial arterial occlusion, but when there is occlusion of the middle cerebral artery, prevention of ischemic damage relies on cortical collaterals. These anatomical and physiological differences underlie the increased risk of stroke with intracranial revascularization and highlight the point that it is not just the safety of a given device, but the safety of the procedure itself, that must be con-