News and Views From the Literature

New Oral Anticoagulants for Atrial Fibrillation: the Factor Xa Inhibitors Rivaroxaban and Apixaban

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Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation

Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators
N Engl J Med. 2011;365:883-891.

Apixaban Versus Warfarin in Patients With Atrial Fibrillation

Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators
N Engl J Med. 2011;365:981-992.

Two landmark trials in which oral factor Xa inhibitors were compared with warfarin anticoagulation in patients with nonvalvular atrial fibrillation (AF) were published in 2011: the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial, which compared rivaroxaban to warfarin, and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, a comparison of apixaban and warfarin. Monitoring levels of either medication is unnecessary; each provides a small decrease in the rate of hemorrhagic stroke and fatal bleeding, and the method of reversing the anticoagulant effect is unclear and not addressed in these studies.

ROCKET AF was a randomized, double-blind trial comparing oral rivaroxaban, 20 mg/d (or 15 mg/d in patients with a creatinine clearance [CrCl] of 30-49 mL/min) to dose-adjusted warfarin (target international normalized ratio [INR] of 2.0-3.0) in 14,264 patients with nonvalvular AF who were at least at moderate risk for stroke (history of stroke, transient ischemic attack [TIA], or systemic embolism or $CHADS_2$ [Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke/TIA] score of at least 2). Notable exclusion criteria detailed in the supplementary appendix were chronic aspirin therapy at >100 mg/d or aspirin plus a thienopyridine (although thienopyridine monotherapy was allowed), need for chronic nonsteroidal anti-inflammatory drug therapy, a calculated CrCl of < 30 mL/min (calculated via the Cockcroft-Gault formula), conditions other than

AF that required anticoagulation, and hemodynamically significant mitral stenosis. ROCKET AF was a noninferiority trial with a composite outcome of stroke (ischemic or hemorrhagic) or systemic embolism. The principal safety endpoint was a composite of clinically relevant bleeding events.

The median age of study participants in ROCKET AF was 73 years, 40% of the patients were women, and the mean $CHADS_2$ score was 3.5. Patients randomized to the warfarin group had INR values in the therapeutic range 58% (median value) of the time, a relatively low rate versus a median value of 66% in the ARISTOTLE trial. In both primary analyses, rivaroxaban was noninferior to warfarin for the primary endpoint of stroke or systemic embolism. In the per-protocol population, a group that included patients who received at least one dose of a study drug and were followed for outcome events only during the treatment period or within 2 days after the last dose (a less stringent test for noninferiority compared with the intention-to-treat [ITT] analysis), the primary endpoint occurred in 188 patients in the rivaroxaban group (1.7% per year) versus 241 in the warfarin group (2.2% per year; hazard ratio [HR] in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66-0.96; $P < .001$ for noninferiority). In the ITT analysis, the primary endpoint occurred in 269 patients in the rivaroxaban group (2.1% per year) versus 306 patients in the warfarin group (2.4% per year; HR, 0.88; 95% CI, 0.74-1.03; $P < .001$ for noninferiority; $P = .12$ for superiority). Clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) versus 1449 in the warfarin group (14.5% per year; HR, 1.03; 95% CI, 0.96-1.11; $P = .44$). There was a significant reduction in intracranial hemorrhage (0.5% vs 0.7%; $P = .02$) and fatal bleeding (0.2% vs 0.5%; $P = .003$) in the rivaroxaban group.

ARISTOTLE was a randomized, double-blind trial comparing oral apixaban, 5 mg twice daily, with dose-adjusted warfarin (target INR, 2.0-3.0) in 18,201 patients with AF and at least one additional risk factor for stroke. Of note, oral twice-daily apixaban, 2.5-mg, was administered to a subset of patients with two or more of the following criteria: age $\geq$ 80 years, weight $\leq$ 60 kg, or serum Cr level $\geq$ 1.5 mg/dL (the formula used to calculate CrCl was not identified). Notable exclusion criteria were the need for aspirin at a dose $\geq$ 165 mg/d or aspirin plus clopidogrel, moderate to severe mitral stenosis, conditions other than AF that required anticoagulation, such as a prosthetic heart valve, and significant renal dysfunction (serum Cr level of $>$ 2.5 mg/dL or calculated CrCl of $<$ 25 mL/min). As with ROCKET AF, ARISTOTLE was a noninferiority trial with a composite primary outcome of stroke (ischemic or hemorrhagic) or systemic embolism; the primary safety outcome was major bleeding. Secondary outcomes that were tested for superiority were the primary outcome criteria and death from any cause.

The median age of study participants was 70 years, 35.3% of the patients were women, 4% of the patients had experienced a fall in the previous year, and the mean $CHADS_2$ score was 2.1. Patients randomized to the warfarin group had INR values in the therapeutic range 66% (median value) of the time. The rate of the primary outcome of stroke or systemic embolism was 1.27% per year in the apixaban group versus 1.60% per year in the warfarin group (HR with apixaban, 0.79; 95% CI, 0.66-0.95; $P < .001$ for noninferiority; $P = .01$ for superiority). The rate of major bleeding was 2.13% per year in the apixaban group versus 3.09% per year in the warfarin group (HR, 0.69; 95% CI, 0.60-0.80; $P < .001$), and the rates of death from any cause were 3.52% in the apixaban group and 3.94% in the warfarin group (HR, 0.89; 95% CI, 0.80-0.99; $P = .047$). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group versus 0.47% per year in the warfarin group (HR, 0.51; 95% CI, 0.35-0.75; $P < .001$), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (HR, 0.92; 95% CI, 0.74-1.13; $P = .42$).

Overall, ROCKET AF enrolled a higher risk group than ARISTOTLE based on age and $CHADS_2$ scores. Warfarin was used more skillfully in ARISTOTLE than in ROCKET AF. Would rivaroxaban still have been noninferior to warfarin had patients randomized to warfarin been in the therapeutic window for a higher percentage of the trial? Alternatively, if rivaroxaban had been dosed twice daily would it have been more effective at preventing the primary outcome? Rivaroxaban was noninferior whereas apixaban was superior to warfarin for the primary outcome of stroke and systemic embolism and both medications exhibited an improved bleeding profile compared with warfarin. In both trials, hemorrhagic strokes were included in the primary efficacy and safety endpoints. Although both medications decreased the rate of hemorrhagic stroke compared with warfarin, the rate of ischemic stroke was not significantly different.

If a patient requiring anticoagulation for AF is already well controlled on warfarin, the small incremental benefit of switching to an oral factor Xa or direct thrombin inhibitor may not be worth the added expense, although the lack of monitoring is certainly more convenient. The ideal patients for these warfarin

alternatives include those who do not tolerate warfarin, are difficult to maintain in the therapeutic INR range, or those who have suffered a thrombotic or bleeding complication while on warfarin. Given the size of the potentially indicated population, informative economic data will be required before there is a general recommendation to use these drugs in AF. At this point, rivaroxaban and dabigatran are US Food and Drug Administration (FDA)-approved for anticoagulation of patients with nonvalvular AF and the FDA is currently reviewing an application for approval of apixaban for this indication. ■

Atherosclerosis

Effects of Evacetrapib Administered as Monotherapy or in Combination With Statins

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Effects of the CETP Inhibitor Evacetrapib Administered as Monotherapy or in Combination With Statins on HDL and LDL Cholesterol: A Randomized Controlled Trial

Nicholls SJ, Brewer HB, Kastelein JJ, et al.
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Significant progress has been made in prevention and treatment of adverse cardiovascular outcomes, including myocardial infarction. Reduction in low-density lipoprotein (LDL) cholesterol levels, specifically with statin-based therapy, has been among the most important treatments for patients with atherosclerotic heart disease. Despite therapeutic advances, recent trials have demonstrated that approximately 20% to 25% of patients with an acute coronary syndrome will have a major cardiovascular event or die in the next 24 months.[1] These results were obtained and have been corroborated in randomized trial populations in which use of standard of care therapies is high (eg, antiplatelets, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and intensive statin therapy).

Among the known risk factors, high-density lipoprotein (HDL) cholesterol has long been considered a target for therapy. Data from the Framingham Heart Study have demonstrated a powerful inverse relationship between HDL concentration and risk of adverse cardiovascular events (ie, low HDL correlating with high risk and vice versa).[2] A post hoc analysis of the Treating to New Targets study demonstrated that HDL levels are inversely associated with cardiovascular events in patients treated with statin therapy, regardless of the achieved LDL level (including $<$ 70 mg/dL).[3] Based on these studies and other data, HDL has become a secondary target for patients who have achieved guideline-based LDL levels. What has yet to be proven is whether lifestyle or pharmacologic intervention to raise HDL is effective in primary or secondary prevention of cardiovascular disease. Because low HDL is prevalent in conditions such as obesity, glucose intolerance, smoking, sedentary lifestyle, and other known and possibly unknown risk factors, it may be that these conditions, not low HDL concentrations, lead to the elevation in risk seen in epidemiologic studies.

The ability to test the benefit of raising HDL pharmacologically has been limited by the potency of our current therapies. Niacin only results in a 20% to 25% increase in HDL, yet it is our most effective therapy. The drug is associated with side effects that limit its tolerability at its most potent doses. After the early stoppage of the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial, controversy regarding the benefits of niacin on clinical outcomes exists.[4] The Treatment of High-Density Lipoprotein to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study, which has randomized 25,000 patients with established atherosclerotic disease to either placebo or niacin, 2 g/d, in combination with laropiprant (a prostaglandin antagonist that has been demonstrated to reduce the intensity and frequency of niacin-induced flushing), will provide more definitive evidence as to the benefits of niacin.[5]

Cholesteryl ester transfer protein (CETP) inhibitors raise HDL by a different mechanism (Figure 1). CETP originally was identified as a potential target for pharmacologic inhibition when it was discovered that individuals with homozygous deficiency of CETP had