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

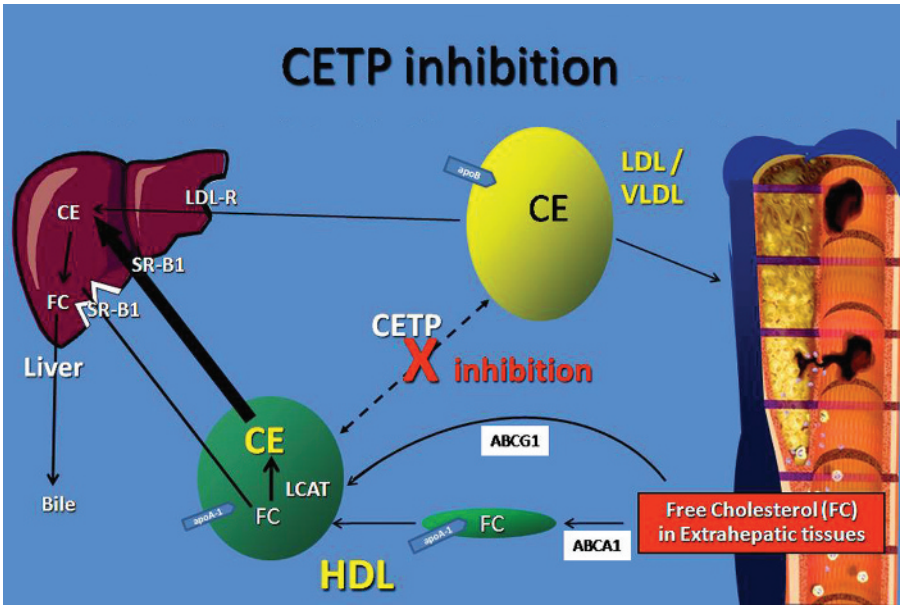

Figure 1. CETP is a plasma that catalyzes the transfer of CE from HDL to Apo B–containing lipoproteins (VLDL and LDL) in exchange for TG. Apo, apolipoprotein; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; FC, free cholesterol; HDL, high-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LDL-R, LDL receptor; SR-B1, scavenger receptor class B1; TG, triglycerides; VLDL, very low-density lipoprotein.

strikingly elevated HDL concentrations of approximately 160 mg/dL.[6] As demonstrated in Figure 1, inhibition of CETP leads to less transfer of cholesteryl esters from HDL to atherogenic particles, potentially leading to increased efflux (transport) of cholesterol from the artery wall to the liver (and out of the body). Animal studies have recently demonstrated that anacetrapib does in fact result in a net efflux of cholesterol.[7] In a rabbit model, attenuation of atherosclerosis was demonstrated with CETP inhibition.[8] Secondary to the dramatic HDL augmentation seen with potent CETP inhibitors such as anacetrapib (138% HDL increase), investigators will now be able to test the benefits of raising HDL by this mechanism.

Torcetrapib was the first CETP inhibitor to be studied in a phase III trial. Despite relative LDL reductions of 24.9% and HDL elevations of 72.1%, the trial was stopped early by the data monitoring committee due to a 25% increase in cardiovascular adverse events and death from any cause.[9] It was also observed that torcetrapib resulted in a mean 5.4-mm Hg increase in systolic blood pressure. Subsequent analysis revealed that this was due to "off-target" effects of torcetrapib on the adrenal gland resulting in elevations of adrenal steroid levels including aldosterone and corticosterone.[10] As a consequence of the torcetrapib failure, the CETP inhibitors dalcetrapib[11,12] and anacetrapib[13] have undergone rigorous safety studies and have been found to have no effect on blood pressure or adrenal steroid hormone production.

Notably, atherosclerotic imaging trials using carotid intima-media thickness[14,15] and intravascular ultrasound (IVUS)[16] had also failed to demonstrate significant reductions in atheroma with torcetrapib treatment. Reassurance to the hypothesis that high levels of HDL may attenuate atheroma progression, or even cause regression, did come from a post hoc analysis of those patients studied by IVUS, however. The quartile that achieved the highest HDL level had evidence of atheroma regression.[17]

The phase II study of evacetrapib, the latest CETP inhibitor, was presented at the American Heart Association 2011 Scientific Sessions. The study was a multicenter, randomized, double-blind, parallel, placebo-controlled clinical trial evaluating the lipid-modifying effects and safety of evacetrapib as monotherapy or in combination with statin therapy. The study randomized 398 patients without documented atherosclerotic disease and either elevated LDL or reduced HDL levels, to one of 10 treatment arms. Evacetrapib, 30 mg/d, 100 mg/d, and 500 mg/d, were evaluated as monotherapy compared with placebo. Evacetrapib, 100 mg/d, was evaluated in combination with atorvastatin, 20 mg/d, simvastatin, 40 mg/d, and rosuvastatin, 10 mg/d, versus statin therapy alone. The study included

TABLE 1

	Monotherapy (Relative Change From Baseline Compared With Placebo)		
	Evacetrapib, 30 mg/d	**Evacetrapib, 100 mg/d**	**Evacetrapib, 500 mg/d**
LDL	−17.6 (−24.6 to −10.5)	−26.2 (−33.2 to −19.2)	−39.8 (−47.0 to −32.7)
HDL	56.7 (43.6 to 69.8)	97.6 (84.5 to 110.8)	131.9 (118.5 to 145.2)
	Combination Therapy: Evacetrapib + Statin (Relative Change From Baseline Compared With Statin Alone)		
	Atorvastatin, 20 mg/d	**Simvastatin, 40 ng/d**	**Rosuvastatin, 10 mg/d**
LDL	−13.9 (−21.2 to −6.7)	−11.2 (−18.3 to −4.2)	−13.5 (−20.6 to −6.4)
HDL	78.5 (64.9 to 92.1)	79.3 (66.2 to 92.4)	88.5 (75.2 to 101.8)

A mixed model for repeated measurements was used to evaluate the percentage change from baseline in efficacy laboratory measurements. Percentage changes are least-squares mean percentage changes from baseline until last follow-up visit from analysis of covariance model. Displayed above are relative percentage changes between placebo and evacetrapib treatment arms. Parentheses include the 90% confidence intervals.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Data from Nicholls SJ et al.[18]

a 12-week treatment phase with a follow-up 4 to 6 weeks after study drug cessation.[18]

The primary lipid results, shown in Table 1, were performed in the modified intention-to-treat population. The results reflect the change in LDL and HDL from baseline to 12 weeks. In addition, at the 500-mg monotherapy dose, a relative decrease of 25.6% in apolipoprotein (Apo) B and increases of 50.0%, 18.8%, and 74.6% in Apo A-I, Apo A-II, and Apo E, respectively, were demonstrated. The effect on lipoprotein(a) was not reported.[18] Evacetrapib was well tolerated without a significant increase in adverse events; importantly, no change in transaminases, creatinine, aldosterone, cortisol, or blood pressure was seen.[18]

In conclusion, Nicholls and colleagues demonstrated not only the adequate safety profile of evacetrapib, but also its lipid-modifying effects as monotherapy and in combination with statins. Of note, the dose of evacetrapib was correlated with the degree of CETP inhibition and resultant LDL reduction and HDL augmentation. The 500-mg dose produced effects similar to those seen with anacetrapib, whereas the 30-mg dose exhibited effects similar to torcetrapib. It is yet unclear whether specific drug properties of the individual CETP inhibitors, reversible versus irreversible mechanisms of CETP inhibition, or the degree (moderate verses potent) of inhibition will prove most important to their effects on atherosclerotic outcomes. This trial has set the stage for a phase III trial of evacetrapib. Along with dalcetrapib and anacetrapib, evacetrapib may prove to be a powerful agent in reducing the future impact of atherosclerotic cardiovascular disease. ■

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