Rivaroxaban did not meet the criteria for superiority in reducing stroke and non-CNS embolism compared with warfarin in patients in the intent-to-treat (ITT) analysis that also included noncompliant patients (2.12 vs 2.42; p=0.117). Among patients who remained on treatment during the trial, rivaroxaban did significantly reduce the primary endpoint (1.70 vs 2.15; p=0.015).

In the per-protocol analysis of event rates, rivaroxaban also reduced the combined endpoint of vascular death, stroke, and embolism compared with warfarin (3.11 vs 3.63; p=0.034), as well as the individual endpoints of hemorrhagic stroke (0.26 vs 0.44; p=0.024) and non-CNS embolism (0.04 vs 0.19; p=0.003). There was also a trend toward reduced all-cause mortality in the rivaroxaban group compared with placebo (1.87 vs 2.21; p=0.073). In an ITT analysis, however, rivaroxaban remained superior to placebo only with regard to hemorrhagic stroke reduction (0.26 vs 0.44; p=0.012). Rivaroxaban had no effect on ischemic stroke relative to warfarin in the on-treatment (1.34 vs 1.42; p=0.581) or ITT analysis (1.62 vs 1.64; p=0.916).

Patients in the rivaroxaban and warfarin groups had similar overall rates of major and nonmajor clinically relevant bleeding (14.9 vs 14.5; p=0.44). However, rivaroxaban significantly reduced the risk of intracranial bleeding, with 55 events in the rivaroxaban group and 84 events in the warfarin group (p=0.019). Moreover, although the overall event rate for major bleeding was similar in the rivaroxaban and the warfarin groups (3.60 vs 3.45; p=0.58), rivaroxaban significantly reduced the risk of death that was caused by major bleeding (0.24 vs 0.48; p=0.003). Conversely, rivaroxaban increased the risk of transfusion (1.65 vs 1.32; p=0.044) and hemoglobin reduction ≥2 g/dL (2.77 vs 2.26; p=0.019).

Patients reported adverse events with similar frequency in the rivaroxaban and warfarin groups, including any serious adverse event (37.3% vs 38.2%) and any adverse event that led to study drug discontinuation (15.7% vs 15.2%).

Rivaroxaban joins dabigatran as another potential alternative for standard anticoagulation with warfarin therapy in patients who are at risk for stroke, investigators said. Rivaroxaban was given as a once-daily agent in this trial and is a factor Xa inhibitor, while dabigatran is a direct thrombin inhibitor that was given twice daily in RE-LY. Dabigatran 150 mg BID (75 mg BID for severe renal impairment) was recently approved by the US Food and Drug Administration for the prevention of stroke and systemic embolism in patients with AF. Rivaroxaban has been approved for use in DVT/PE and is currently under review for use in AF.

DEFINE: CETP Inhibition With Anacetrapib Significantly Raises HDL Cholesterol and Further Lowers LDL

Cholesteryl ester transfer protein (CETP) inhibition can raise high-density lipoproteins (HDLs) and, in some cases, lower low-density lipoproteins (LDLs). Development of the first CETP agent to be evaluated in a Phase 3 clinical trial—torcetrapib—was stopped, however, when it was found to be associated with increased mortality and cardiovascular events [Barter PJ et al. *N Engl J Med* 2007]. Christopher P. Cannon, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, reported results from the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE; NCT00685776) trial, which showed that anacetrapib safely and substantially lowered LDL-C and raised HDL-C levels in patients with coronary heart disease (CHD).

DEFINE was a Phase 2, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of anacetrapib in patients with CHD or CHD risk equivalents (Framingham Risk Score >20%). In addition to the CHD requirement, participants were required to be aged between 18 and 80 years and have LDL-C ≥50 but ≤100 mg/dL, HDL-C <60 mg/dL, and triglycerides (TG) ≤400 mg/dL.

The primary study endpoints were the percentage change from baseline in LDL-C after 24 weeks of treatment and the safety and side effect assessments through 76 weeks. Key efficacy endpoints included HDL-C, apoB, apoA1, non-HDL-C, and TG levels at Weeks 24 and 76 and LDL-C at Week 76. Subjects (mean age 63 years, 78% men) were randomly assigned to receive 100 mg anacetrapib (n=811) or placebo (n=812) once daily for 18 months, followed by a 3-month poststudy follow-up.

At Week 6, LDL-C levels decreased by 40% (p<0.001) and HDL-C levels increased by 138% (p<0.001) compared with placebo (Figure 1). Effects on other lipid parameters are shown in Table 1. Anacetrapib did not exhibit the adverse cardiovascular effects that have been seen with torcetrapib, including changes in blood pressure, electrolyte disturbances, and elevations in aldosterone levels. Cardiovascular events occurred in 16 patients in the anacetrapib group (2.0%) and 21 patients who received placebo (2.6%; p=0.40). Using Bayesian analysis, the investigators determined that this event distribution indicated a 94% predictive probability that anacetrapib would not be associated

with the 25% increase in cardiovascular adverse events that was seen with torcetrapib. Furthermore, the composite of all-cause death, MI, unstable angina, stroke, or revascularization was lower in the anacetrapib group (3.3%) compared with the placebo group (5.3%; p=0.048). This was mostly attributed to a lower rate of revascularization with anacetrapib (1.0% vs 3.5%; p<0.001).

Figure 1. Effects on LDL-C and HDL-C.

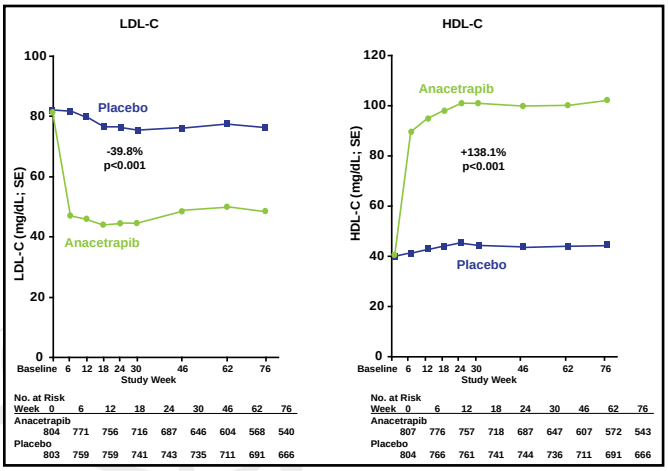

Table 1. Other Lipid Parameters.

Parameter	Change from Baseline Beyond That with Placebo 95% CI	
	Week 24	Week 76
Non-HDL-C	-31.7* (-33.6, -29.8)	-29.4* (-31.6, -27.3)
ApoB	-21.0* (-22.7, -19.3)	-18.3* (-20.2, -16.4)
ApoA1	44.7* (42.8, 46.5)	42.3 (40.5, 44.1)
TC	13.7* (12.0, 15.3)	15.6* (13.8, 17.3)
TG	-6.8 (-9.9, -3.9)	-5.3 (-8.9, -1.7)
Lp(a)	-36.4 (-40.7, -32.3)	-38.8 (-44.5, -33.9)

*p<0.001; mean for all variables except for triglycerides, lipoprotein (a), for which medians are shown.

"This drug has profound effects on HDL going to new highs and with LDL going to additional lows," Dr. Cannon remarked in an interview. Additional, larger studies, soon to be initiated, are needed to establish the clinical benefit of anacetrapib, expand the ethnic diversity of the study population, and provide more insight into the long-term safety of reducing LDL-C to extremely low levels.

Thomas F. Lüscher, MD, University of Zurich, Zurich, Switzerland, discussed the design and results of the DEFINE trial. He concluded the trial was well designed and that CETP inhibition with anacetrapib resulted in impressive changes in lipid profile beyond those that were achieved with statins without increasing blood pressure. He further stated, however, "It remains to be shown that the HDL particles during treatment with anacetrapib are biologically normal."

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Benefits of Inducing ApoA1 Synthesis Still Unclear: Results From ASSERT

Reducing adverse cardiovascular events through improving reverse cholesterol transport has become an active area of research. While raising high-density lipoprotein cholesterol (HDL-C) remains a major focus, increasing the synthesis of apolipoprotein A1 (apoA1), the primary cholesterol transport protein that is associated with HDL-C, has been suggested as an alternative approach. Stephen J. Nicholls, MD, PhD, Cleveland Clinic, Cleveland, Ohio, USA, presented data from a Phase 2 study that was designed to test whether treatment with RVX-208, an oral drug that induces apoA1 synthesis, would lead to increased apoA1 levels. While an increase in levels of apoA1 was observed across the dosing range of RVX-208, treatment with RVX-208 at individual doses did not significantly increase apoA1 levels compared with placebo.

The primary objectives of the ApoA1 Synthesis Stimulation Evaluation in Patients Requiring Treatment for Coronary Artery Disease (ASSERT; NCT01058018) study were to evaluate the efficacy, tolerability, and safety of oral RVX-208 in patients with stable coronary artery disease. This was a double-blind, randomized, controlled phase 2 trial in 299 patients who were receiving stable statin therapy for at least 30 days and treated for 12 weeks with RVX-208 (50, 100, or 150 mg twice daily) or placebo. Patients had a mean age of 65.8 years and were mostly white men and hypertensive; 29.4% were diabetic, and 17.1% smoked. Baseline HDL-C and apoA1 were 44 mg/dL and 141 mg/dL, respectively.

The primary study outcome was the percentage change in apoA1 from baseline to 12 weeks for each treatment arm compared with placebo. Secondary outcomes were comparisons of the dose- and time-response relationships for apoA1, total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), non-HDL-C, triglycerides, apoB, and LDL and HDL subclasses over 4, 8, and 12 weeks.

After 12 weeks, there was no statistically significant difference in the increase in apoA1 levels between subjects who were treated with any individual dose of RVX-208