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.

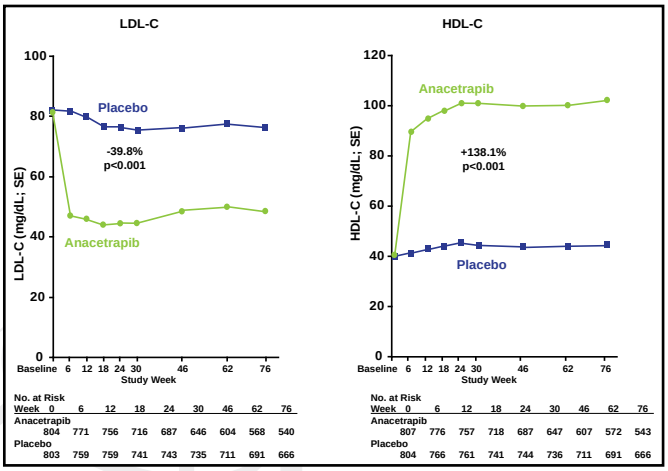

Table 1. Other Lipid Parameters.

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.

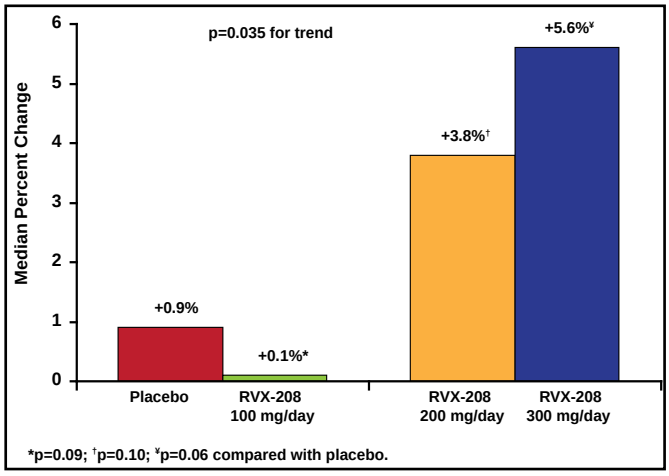
The primary objectives of the ApoA1 Synthesis Stimulation Evaluation in Patients Requiring Treatment for Coronary Artery Disease (ASSERT; NCT01058018) study were to evaluate the efficacy, tolerability, and safety of oral RVX-208 in patients with stable coronary artery disease. This was a double-blind, 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

compared with placebo (+5.6% in the 300 mg/day group [p=0.06]; +3.8% in the 200 mg/day group [p=0.10]; and +0.1% in the 100 mg/day group [p=0.09]; Figure 1). However, a dose-dependent increase in apoA1 levels was observed across the dosing range [p=0.035]. RVX-208 produced significantly increased HDL-C levels at the two higher dose levels (+6.3% at the 200-mg/day dose [p<0.05] and +8.3% at 300 mg/day [p<0.01]) but not at the 100-mg/day dose. Although there was no increase in the number of HDL particles, the size of the particles appeared to change, with a preferential increase in the larger HDL particles by up to 21% at the highest dose (p<0.001 versus placebo). There was also a significant (p<0.05) increase in the amount of α1 HDL at the higher doses. There was no change in LDL-C, triglycerides, apoB, or hsCRP.

Figure 1. Median Change in ApoA-1 From Baseline.



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Rates of increased ALT/AST levels were higher for each dose of RVX-208 compared with placebo, with 3 patients in the 100 mg/day group, 8 patients in the 200 mg group, and 7 patients in the 300 mg group having ALT/AST >3 xULN (p=0.009). A total of 8 patients had ALT/AST >8 xULN. The liver enzyme increases were reversible, and there was no evidence of liver damage.

"The changes in apoA1, HDL-C, and large HDL particles are consistent with enhanced mobilization of lipids into functional HDL particles and reversible transaminase elevations," Dr. Nicholls said, thus establishing proof of concept. He also noted that most of the benefits of RVX-208 were seen during Weeks 8 to 12, indicating that longer treatment may have provided an increased benefit. However, the increases in AST/ALT that were seen in this study deserve careful prospective evaluation in future longer-term studies and could limit the clinical utility of this compound.

BASKET-PROVE: DES Just as Safe as BMS in Large Coronary Vessels

Drug-eluting stents (DES) confer no additional late cardiovascular risk in patients with stenting of large coronary arteries when compared with bare-metal stents (BMS), reported Christoph Kaiser, MD, University Hospital, Basel, Switzerland. Prof. Kaiser presented the results of the 24-month Basel Stent Cost-effectiveness Trial-PROspective Evaluation Examination (BASKET-PROVE; ISRCTN72444640).

The trial was designed to test the hypothesis that in large coronary arteries, first-generation DES provide only a small reduction in target vessel revascularization (TVR) and may increase late cardiac death/myocardial infarction (MI). This study was designed after a retrospective analysis of the single-center BASKET—Late Thrombotic Events (BASKET-LATE) trial, which examined the difference between first-generation DES and BMS among 826 patients, demonstrated that DES were associated with an increase in cardiac-related deaths or non-fatal MI after 6 months in patients with stenting of *large* vessels. Of note, no such association was found in patients with *small* vessels, however (Pfisterer M et al. *Eur Heart J* 2009), for which DES remain the stent of choice. A secondary aim of BASKET-PROVE was to determine whether a similar risk-benefit relationship would also be found for second-generation DES.

The study enrolled 2314 patients with vessels 3 mm in diameter and divided them into 3 groups: sirolimus-eluting (first-generation; SES) DES (n=775), everolimus-eluting (second-generation; EES) DES (n=774), and BMS (n=765). The mean patient age was 66 years, and 18% were diabetic. Patients represented a typical population that required stenting, with two-thirds presenting with acute coronary syndromes (34% with STEMI) and the remainder with stable chronic coronary artery disease. Patients were placed on aspirin therapy (75-100 mg daily) indefinitely and on clopidogrel 75 mg daily for a minimum of 1 year.

Compliance with dual antiplatelet therapy was high (82%) at 1 year. After 2 years, there was no significant difference in the primary endpoint of cardiac death or nonfatal MI between the groups (2.6% for SES, 3.2% for EES, and 4.8% for BMS; p=0.13 SES vs BMS and p=0.37 EES vs BMS).

Also, there were no significant differences in the secondary endpoints of total death, noncardiac death, or stent thrombosis. However, there was a statistically