fatty acids producing lysophosphatidylcholine and oxidized nonesterified fatty acids, explained Prof. White. "Unstable" plaques are characterized by a higher content of Lp-PLA_2 and other markers of inflammation [Corson MA et al. *Am J Cardiol* 2008].

Darapladib decreases Lp-PLA_2 levels by ~60% [Serruys PW et al. *Circulation* 2008]. In preclinical investigations, it reduced Lp-PLA_2 levels and necrotic core area within atherosclerotic plaque [Wilensky RL et al. *Nat Med* 2008]. In humans, treatment with darapladib was shown to halt progression of coronary artery necrotic plaque core volume in patients with CHD, but not atheroma volume [Serruys PW et al. *Circulation* 2008].

STABILITY compared darapladib at a dosage of 160 mg/day with placebo in a double-blind, randomized, global trial of 15,828 patients with chronic CHD receiving standard of care. The median patient age was 65 years, ~80% were white, and ~80% were male. Fifty-nine percent had a qualifying diagnosis of MI for more than 1 month prior to randomization and 75% had undergone prior coronary revascularization. Fifteen percent had multivessel CHD at baseline. Very high rates of evidence-based background therapies were used at baseline and throughout the duration of the study (>90% use of aspirin; >95% use of statins; ~80% use of β-blockers; and ~50% use of angiotensin-converting enzyme inhibitors).

At a median follow-up of 3.7 years, the primary endpoint—a composite of CV death, MI, and stroke—occurred in 819 patients randomized to placebo (10.4%) compared with 769 patients randomized to darapladib (9.7%), corresponding to a hazard ratio of 0.94 (95% CI, 0.85 to 1.03) that did not achieve significance (p=0.20). Results for the components of the primary endpoint are shown in Table 1. There were no significant differences between darapladib and placebo on any of the individual components of the primary endpoint or all-cause mortality.

Coronary-specific endpoints suggested benefit to darapladib. Darapladib was associated with a reduction in the rate of the prespecified secondary endpoints of major coronary events (10.3% vs 9.3%; HR, 0.90; p=0.045) and total coronary events (16.1% vs 14.6%; HR, 0.91; p=0.019; Table 1). These findings should be considered exploratory in light of the lack of effect on the primary endpoint, said Prof. White.

Serious adverse events occurred at a similar frequency in the darapladib and placebo arms, 42.6% and 43.7%. Adverse events leading to study drug discontinuation occurred in 19.8% and 13.5% in the darapladib and placebo arms, respectively. Side effects that led to darapladib discontinuation included diarrhea, abnormal feces, abnormal skin odor, and abnormal urine odor.

Table 1. Cardiovascular and Mortality Endpoints

	Placebo	Darapladib	HR (95% CI)	p Value
CV death	4.7%	4.5%	0.96 (0.83, 1.11)	0.59
MI	5.1%	4.6%	0.89 (0.77, 1.03)	0.11
Stroke	1.9%	1.9%	1.01 (0.81, 1.27)	0.92
All-cause mortality, MI, stroke	12.2%	11.7%	0.96 (0.88, 1.05)	0.40
All-cause mortality	7.3%	7.3%	1.01 (0.90, 1.13)	0.87
Major coronary events (CHD death, MI, urgent coronary revascularization)	10.3%	9.3%	0.90 (0.82, 1.00)	0.045
Total coronary events (CHD death, MI, any coronary revascularization, hospitalization for unstable angina)	16.1%	14.6%	0.91 (0.84, 0.98)	0.019

CHD=coronary heart disease; CV=cardiovascular; MI=myocardial infarction.

In STABILITY, subgroup analyses based on biomarkers and genetics will further explore the potential utility of darapladib in specific high-risk patient subsets. The SOLID TIMI-52 trial [NCT010007277] which is testing darapladib in ~13,000 post-ACS patients is expected to report results in 2014.

Monoclonal Antibody Reduces LDL-C in Presence of Statin (LAPLACE-2)

Written by **Wayne Kuznar**

A fully human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), when added to background statin therapy, reduces levels of low-density lipoprotein cholesterol (LDL-C) in patients with hypercholesterolemia and mixed dyslipidemia.

The monoclonal antibody evolocumab (previously AMG 145), which inhibits PCSK9, dramatically lowered levels of LDL-C in Phase 2 clinical trials when administered alone or in combination with a statin, including among patients intolerant of statin therapy, those with familial hypercholesterolemia, and in those treated in a 52-week study [Koren MJ et al. *Circulation* 2013; Giugliano RP et al. *Lancet* 2012; Koren MJ et al. *Lancet* 2012; Raal F et al. *Circulation* 2012; Sullivan D et al. *JAMA* 2012]. These observations led to the randomized, multicenter, placebo-controlled, double-blind Phase 3 LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy-2 study [LAPLACE-2; NCT01763866], the results of which were presented by Jennifer G. Robinson, MD, MPH, University of Iowa, Iowa City, Iowa, USA.

The efficacy and safety of evolocumab were assessed in 1896 patients with primary hypercholesterolemia and mixed dyslipidemia (LDL-C ≥80 mg/dL) who were also taking a high- or moderate-intensity statin. Patients were eligible for the study if they had a central laboratory fasting LDL-C at screening of ≥150 mg/dL (4.0 mmol/L; no statin at screening), ≥100 mg/dL (2.6 mmol/L; nonintensive statin at screening), or ≥80 mg/dL (2.1 mmol/L; intensive statin at screening). The primary objective of this study was to evaluate the efficacy (vs placebo) of 12 weeks of subcutaneous (SC) evolocumab administered every 2 weeks or every month when used in combination with a daily statin with or without ezetimibe on percent change from baseline in LDL-C.

Patients were initially randomized to high (atorvastatin 80 mg or rosuvastatin 40 mg) or moderate (atorvastatin 10 mg, rosuvastatin 5 mg, or simvastatin 40 mg) intensity statin therapy. Following a 4-week stabilization period, patients randomized to atorvastatin 10 or 80 mg were then randomized to 1 of 6 treatment groups: SC evolocumab 140 mg Q2W and oral placebo QD; SC evolocumab (420 mg) QM and oral placebo QD; SC placebo Q2W and oral placebo QD; SC placebo QM and oral placebo QD; SC placebo Q2W and ezetimibe 10 mg QD; or SC placebo QM and ezetimibe 10 mg QD. Patients randomized to rosuvastatin or simvastatin were then randomized to 1 of 4 treatment groups: evolocumab Q2W, evolocumab QM, SC placebo Q2W, or SC placebo QM.

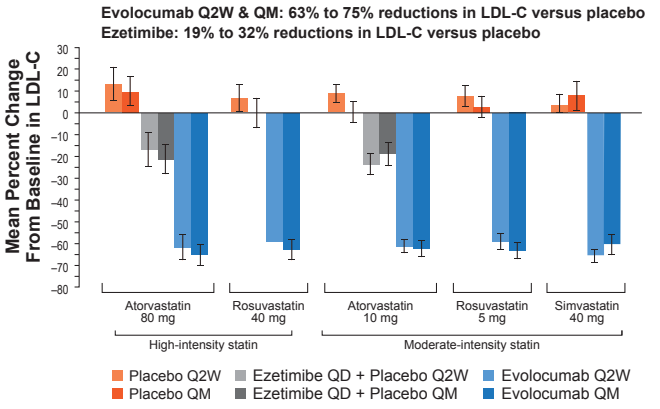
Overall, 1896 patients were randomized, mean patient age was 60 years, ~20% had coronary artery disease, ~10% had peripheral arterial disease or cerebrovascular disease, and ~16% had type 2 diabetes. Their mean baseline LDL-C was ~110 mg/dL (2.85 mmol/L). When combined with either a high- or moderate-intensity statin, evolocumab-treated groups showed highly significant reductions in LDL-C versus placebo of 63% to 75% (Figure 1). Compared with placebo, ezetimibe when combined with atorvastatin reduced levels of LDL-C by 19% to 32%. An LDL-C level <70 mg/dL was achieved by 86% to 94% of evolocumab recipients on a moderate-intensity statin and 93% to 95% on a high-intensity statins.

Adding evolocumab to moderate-intensity statin regimens reduced LDL-C levels to a mean of 38 to 45 mg/dL (0.98 to 1.16 mmol/L), and to 35 to 38 mg/dL (0.09 to 0.98 mmol/L) with high-intensity statin regimens.

Compared with placebo, evolocumab also significantly reduced levels of non-high-density lipoprotein cholesterol by 58% to 65%, apolipoprotein B by 51% to 59%, and lipoprotein (a) by 21% to 36%.

There were no notable differences in safety and tolerability in evolocumab-, placebo-, and ezetimibe-treated patients.

Figure 1. LDL-C Response at Mean of Weeks 10 and 12



LDL-C=low-density lipoprotein cholesterol.

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Higher Rate of Device Success With Balloon-Expandable Transcatheter Aortic Valve (CHOICE)

Written by **Wayne Kuznar**

In the first head-to-head randomized comparison of two devices used for transcatheter aortic valve replacement (TAVR) in high-risk patients with severe aortic stenosis (AS), a balloon-expandable transcatheter valve was found to have a higher rate of device success than a self-expanding valve.

Data from the Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIEN XT trial [CHOICE; Abdel-Wahab M et al. *JAMA* 2014], were presented by Mohamed Abdel-Wahab, MD, Academic Teaching Hospital of the Universities of Kiel and Hamburg, Bad Segeberg, Germany.

The primary objective of CHOICE was to compare the procedural success of the two valves in patients with symptomatic severe AS who were at high surgical risk or deemed inoperable. Procedural success was defined as successful vascular access, deployment of the device, retrieval of the delivery system, correct position of the device, intended performance of the heart valve without moderate or severe regurgitation, and only one valve implanted in the proper anatomical location. The combined safety endpoint was a composite of all-cause mortality, major stroke, life-threatening or disabling bleeding, acute kidney injury Stage 3 (including renal replacement therapy), periprocedural myocardial infarction, major vascular complications and repeat procedure for valve-related dysfunction.