death, nonfatal myocardial infarction (periprocedural or spontaneous), definite or probable stent thrombosis, stroke, or PLATO major bleeding. The noninferiority margin was set at 0.75% absolute. In other words, the study had 90% power to show that the rate of the net clinical outcome in patients who were assigned TAPT was not more than 0.75% higher than with DAPT, assuming that no difference in rates between the regimens truly existed.

Patients were well balanced between treatment assignments. The mean age was 63 years; one-third of subjects were women, one-third was diabetic, and one-third of subjects were current smokers. Approximately 50% of patients presented with an acute coronary syndrome (unstable angina or non-ST-segment elevation myocardial infarction [NSTEMI]), and 10% presented with STEMI. Concomitant use of beta-blockers (68%), statins (85%), and ACEI/ARB (65%) was frequent.

Thirty-five days after randomization, 1.44% of DAPT and 1.22% of TAPT-treated patients experienced the primary endpoint (ie, an absolute risk difference in favor of TAPT of 0.22%; p<0.001 for noninferiority; HR, 0.85; 95% CI, 0.49 to 1.48; p=0.57 for superiority). There were no significant differences between treatment groups when data were analyzed as individual risk components (all incidence rates were <1%), nor were there any differences in the rates of target lesion or vessel revascularization. Platelet reactivity (VerifyNow $P2Y_{12}$ Assay) was significantly (p<0.001) higher after clopidogrel loading and at the end of the study for patients who received the DAPT regimen.

Science Advisor's Note

This study has several limitations that are worthy of emphasizing. Comparing two treatment regimens for short-term noninferiority of a net clinical benefit does not easily lend itself to a clinically meaningful conclusion. In addition, the comparator treatment arm in this trial was one of the regimens that were tested in OASIS-7, which was not significantly different from standard-dose clopidogrel [*MD Conference Express*. ESC Edition 2009]. Thus, it is not clear how the investigational TAPT maintenance regimen compares with standard-dose DAPT post-DES. Prof. Kim cautioned that the event rates were also lower than expected, which biases a noninferiority comparison toward concluding that no difference exists. Since the noninferiority margin (0.75% absolute) was >50% of the observed event rate in the comparator group (1.44%), even a 50% relative increase in the event rate with TAPT (to 2.16%) would not have crossed the noninferiority margin (2.19%). In addition, it is possible that higher-than-anticipated (and differential) nonadherence rates to allocated treatment (13.5% in the DAPT regimen vs 8.4% in the TAPT regimen) biased the results toward the null. Until larger and longer duration trials are conducted with standard comparator groups and primary efficacy outcomes, it remains unclear whether either regimen is effective or safe for routine clinical practice after DES implantation.

New Monoclonal Antibody to PCSK9 Markedly Lowers LDL-C in Patients on Atorvastatin

Written by Rita Buckley

Proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) binds to low-density lipoprotein receptors (LDLRs) and plays a pivotal role in LDLR degradation [McKenney JM et al. *J Am Coll Cardiol* 2012]. James M. McKenney, PharmD, National Clinical Research, Inc., Richmond, Virginia, USA, reported outcomes on the low-density lipoprotein cholesterol (LDL-C)-lowering effects of SAR236553/REGN727 (SAR236553), a highly specific, fully human monoclonal antibody to PCSK9 [Efficacy and Safety Evaluation of SAR236553 (REGN727) In Patients With Primary Hypercholesterolemia and LDL-Cholesterol on Stable Atorvastatin Therapy; NCT01288443].

Three prior Phase 1 studies of SAR236553 have shown that the monoclonal antibody to PCSK9 significantly reduces LDL-C levels in healthy volunteers and in subjects with familial or nonfamilial hypercholesterolemia [Stein EA et al. *N Engl J Med* 2012].

The current Phase 2 dose-ranging study was a double-blind, parallel-group, placebo-controlled, multicenter trial. It included patients aged 18 to 75 years with LDL-C ≥100 mg/dL (2.59 mmol/L) who were on stable-dose atorvastatin at 10 mg, 20 mg, or 40 mg for ≥6 weeks. A total of 183 individuals were randomized to either subcutaneous placebo every 2 weeks (Q2W); SAR236553 at 50 mg, 100 mg, or 150 mg (Q2W); or SAR236553 at 200 mg and 300 mg once every 4 weeks (Q4W) with an alternating placebo injection at 2 weeks.

The primary objective of the study was to evaluate the safety and LDL-C-lowering effect of 12 weeks of treatment with SAR236553 versus placebo. The primary study endpoint was the percentage change in calculated LDL-C from baseline (mean of Week -1 and Week 0) to Week 12.

The addition of SAR236553 resulted in a significant decrease in LDL-C from baseline. A clear dose-response relationship with respect to percentage of LDL-C lowering

for both Q2W and Q4W administration was demonstrated: 40%, 64%, and 72% with 50 mg, 100 mg, and 150 mg Q2W, respectively, and 43% and 48% with 200 and 300 mg Q4W. At Week 12, LDL-C reduction with placebo was 5.1% (Table 1). SAR236553 also increased the rate of achievement of LDL-C goals (<70 mg/dL) compared with placebo. Of note, LDL-C reductions were generally unaffected by the baseline atorvastatin dose.

Table 1. Changes in LDL-C from Baseline to Week 12 by Treatment Group (mITT Population).

Intervention	Baseline LDL-C (mg/dL)	Percent Change LDL-C[1]
Placebo	130.2	-5.1 (3.1)
SAR236553 50 mg Q2W	123.2	-39.6 (3.2)*
SAR236553 100 mg Q2W	127.0	-64.2 (3.1)*
SAR236553 150 mg Q2W	123.9	-72.4 (3.2)*
SAR236553 200 mg Q4W	128.2	-43.2 (3.3)*
SAR236553 300 mg Q4W	131.6	-47.7 (3.2)*

p<0.0001 for percent change SAR236553 versus placebo; [1]LS mean (SE), using LOCF method.

SAR236553 produced consistent and robust reductions in all other Apo B-containing lipoproteins (Table 2), with important decreases in lipoprotein(a)—a finding that is consistent with the prior Phase 1 studies [Stein EA et al. *N Engl J Med* 2012]. There was also a trend toward lower triglycerides and increases in high-density lipoprotein cholesterol (HDL-C) and Apo AI versus placebo—findings that were not entirely explained by the direct mechanism of action of PCSK9 inhibition. The biweekly injections appeared to deliver a more sustained LDL-C reduction over the Q4W dosing schedule.

Table 2. Changes in ApoB, Non-HDL-C, and Lp(a) from Baseline to Week 12 by Treatment Group (mITT Population).

Intervention	% Change Apo B	% change Non-HDL-C	% Change Lp(a)
Placebo	2.2	-2.2	0.0
SAR236553 50 mg Q2W	-27.3*	-33.6*	-13.3†
SAR236553 100 mg Q2W	-48.1*	-55.6*	-26.1*
SAR236553 150 mg Q2W	-56.1*	-62.5*	-28.6*
SAR236553 200 mg Q4W	-28.7*	-37.4*	-16.7†
SAR236553 300 mg Q4W	-33.1*	-40.7*	-7.9†

*p<0.0001 for percent change SAR236553 versus placebo; †p=0.05 for percent change SAR236553 versus placebo; p values are not adjusted for multiplicity (descriptive only).

SAR236553 was well tolerated during the study, with no signs of persistent or prevalent clinical or laboratory adverse events, including those that were associated with hepatic and muscle assessments. One patient who was assigned to the 300-mg Q4W regimen developed a rare complication, leukocytoclastic vasculitis, an inflammatory immune complex-mediated vasculitis of small-caliber blood vessels, although no similar reactions have been reported. No antidrug antibodies were observed 2 weeks before or after the incident.

According to Dr. McKenney, these results support further evaluation of this novel biologic lipid-lowering therapy in large, multicenter, randomized, controlled trials. Plans are underway to evaluate if PCSK9 antibody therapy can reduce adverse cardiovascular outcomes among an internationally diverse patient population who are taking a variety of different background lipid-lowering therapies.

Oral Rivaroxaban Alone for Symptomatic Pulmonary Embolism

Written by Maria Vinall

Rivaroxaban, a direct, specific, competitive factor Xa inhibitor that inhibits thrombin generation, is an effective treatment for venous thromboembolism (VTE). The Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism trial [EINSTEIN PE; Buller HR et al. *N Engl J Med* 2012] reported data that showed that rivaroxaban was noninferior to standard therapy but had a superior bleeding profile in patients with pulmonary embolism (PE). Results were presented by Harry Roger Buller, MD, Academic Medical Center, Amsterdam, The Netherlands.

This was a multicenter, randomized, open-label, assessor-blind, event-driven, noninferiority trial that comprised patients with acute symptomatic PE with or without deep-vein thrombosis (DVT). Patients (n=4832) were randomized to receive open-label oral rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg once daily, versus subcutaneous enoxaparin (1 mg/kg) twice daily for 5 days plus a vitamin K antagonist (VKA; acenocoumarol or warfarin), initiated within 48 hours of randomization. Enoxaparin was discontinued when the patient's international normalized ratio (INR) was ≥2.0 for 2 consecutive days after at least 5 days of enoxaparin treatment. INR was measured at least once a month and the dose of the VKA was adjusted to maintain an INR of 2.0 to 3.0. The study treatment duration was 3, 6, or 12 months, and patients were followed for 30 days post-treatment. The primary efficacy outcome was first