ONSITEINSIGHT®

ON ISSUES IN THE MANAGEMENT OF CARDIOMETABOLIC DISEASES • NOVEMBER 2012

LEARNING OBJECTIVES:

After reading articles in this issue of *OnsiteInsight*®, you should be better able to:

- Discuss the latest clinically relevant data pertaining to the use of pharmacologic and nonpharmacologic treatment options for cardiovascular risk reduction
- Review the implications of new clinical evidence from latebreaking trials assessing treatment options and cardiovascular endpoints, and apply to clinical practice as appropriate
- Review the evidence for the potential efficacy of novel agents for reducing lipid concentrations and atherosclerosis

TARGET AUDIENCE:

This newsletter is designed for primary care physicians, cardiologists, endocrinologists, and other healthcare professionals involved in the management of patients at risk for or with cardiovascular and metabolic diseases.

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OnsiteInsight® provides important reviews of the latest clinically relevant research in diabetes. Some reports may discuss uses for products or devices that are not approved by the US Food and Drug Administration or appropriate regulating body, or are investigational in nature. Such uses will be noted within the body of the article.

The data reported in this issue of *OnsiteInsight*® were presented during the American Heart Association Scientific Sessions 2012 from November 3-7 in Los Angeles, California. CCMDweb.org is reporting on data from the Scientific Sessions. This content has not been peer reviewed. Instances of unpublished data and off-label or investigational uses are disclosed.

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No Difference in CV Events With Dalcetrapib or Placebo for ACS Patients

Results from the Halted dal-OUTCOMES Trial

Data from dal-OUTCOMES found that dalcetrapib did not reduce cardiovascular events any more than placebo in patients with a recent acute coronary syndrome (ACS). Dalcetrapib* is a novel agent of the cholesteryl ester transfer protein (CETP) class of drugs for reducing atherosclerosis risk by improving blood lipid levels.

Gregory G. Schwartz, MD, PhD, presented data from dal-OUTCOMES, a phase III trial of nearly 16,000 patients that evaluated whether CETP inhibition with dalcetrapib would reduce cardiovascular risk among patients with a recent ACS event. The trial was terminated for futility at a prespecified interim analysis that included 1,135 primary endpoint events—71% of projected events. The primary endpoint was a composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, unstable angina, or cardiac arrest with resuscitation.

At the end of 3 years, no difference was found in the incidence of the primary endpoint among patients randomized to dalcetrapib 600 mg qd or placebo. The cumulative event rate was 8.0% for dalcetrapib and 8.3% for placebo (hazard ratio 1.04; 95% confidence interval, 0.93-1.16; *P*=0.52). Dalcetrapib did not exert a significant impact on any component of the primary endpoint or all-cause mortality.

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Novel PCSK9 Inhibitors Show Promise for LDL-C Reduction in Statin-Intolerant Patients

Novel inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) show promise for LDL-C reduction among the 10% to 20% of patients who are statin intolerant, those who may require additional medications for lowering LDL-C to target levels, or patients with primary hypercholesterolemia for whom statins may not be sufficient to achieve target LDL-C. Here, we report on the results of several phase II trials of the PCSK9 inhibitors, AMG 145* and RN316*.

GAUSS trial[1]

In GAUSS (Goal Achievement after Utilizing an anti-PCSK9 antiboty in Statin-intolerant Subjects), a 12-week, randomized, double-blind, placebo- and ezetimibe-controlled, dose-ranging study, the efficacy and tolerability of AMG 145 in patients with statin intolerance due to muscle-related side effects were assessed for the primary endpoint of percentage change in LDL-C. Patients (n=160) were randomized to AMG 145 alone at 280 mg (n=32), 350 mg (n=31), and 420 mg (n=32); and AMG 145 420 mg plus ezetimibe 10 mg (n=20). The control group received placebo plus ezetimibe 10 mg (n=32). AMG 145 and placebo were administered subcutaneously every 4 weeks.

Evan A. Stein, MD, presented data showing that at Week 12, mean changes in LDL-C were:

- -67 mg/dL for 280 mg[1]
- -70 mg/dL for 350 mg
- -91 mg/dL for 420 mg
- -110 mg/dL for 420 mg and ezetimibe
- -14 mg/dL for placebo and ezetimibe

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Physicians' Health Study II: Daily Multivitamins Confer No CV Benefit

Use of a daily multivitamin does not reduce cardiovascular disease (CVD) risk among middle-aged and older men, confirm data from the Physician's Health Study (PHS) II. Over a median follow-up of 11.2 years, no difference was seen in the primary endpoint, a composite of major cardiovascular events, between men who were taking a daily multivitamin or active placebo in the trial. Moreover, multivitamin supplementation had no effect on secondary endpoints, including myocardial infarction (MI) and stroke.

Lead investigator Howard D. Sesso, ScD, MPH, presented the data from PHS II, the only large-scale, double-blind, placebo-controlled trial that evaluated the long-term efficacy of daily multivitamins on major cardiovascular events. A total of 14,641 male physicians (7,641 of whom were from the PHS I cohort) aged ≥50 years were randomized to a daily multivitamin (n=7,317) or placebo (n=7,324).

With respect to the primary endpoint, a total of 1,732 major cardiovascular events occurred. The rates of major cardiovascular events were 11.0 per 1,000 person-years in the multivitamin group and 10.8 per 1,000 person-years in the placebo group.

No. of major cardiovascular events			
Multivitamin (n=7,317)	**Placebo (n=7,324)**	**HR (95% CI)**	***P***
876	856	1.01 (0.91-1.10)	0.91

A similar lack of benefit was seen for secondary and other endpoints. For MI, 3.9 events per 1,000 person-years for multivitamin vs 4.3 events for placebo; for stroke, 4.1 events per 1,000 person-years for multivitamin vs 3.9 events for placebo.

	No. of events			
	Multivitamin (n=7,317)	**Placebo (n=7,324)**	**HR (95% CI)**	***P***
MI	317	335	0.93 (0.80-1.09)	0.39
Stroke	332	311	1.06 (0.91-1.23)	0.48
CVD mortality	408	421	0.95 (0.83-1.09)	0.47
Total mortality	1,345	1,412	0.94 (0.88-1.02)	0.13

The effect of multivitamin supplementation on major cardiovascular events was no different among men with or without CVD history at baseline (*P*=0.62 for interaction), nor among those with or without various risk factors.

No significant adverse effects of daily multivitamin use were found.

In subsequent discussion, Sidney C. Smith, Jr., MD, concluded that PHS II data do not support the use of multivitamins to prevent CVD, noting that the decision to take a multivitamin should be based upon individual need to address nutritional deficiency or other benefits, including a modest reduction in cancer.

Reference:
Sesso HD, et al. Multivitamins in the prevention of cardiovascular disease in men. The Physicians' Health Study II randomized controlled trial. *JAMA*. 2012;308(17):1751-1760.

UMPIRE Calls PolyPill Effective for Improving Adherence, Cholesterol, and Blood Pressure

Results from the UMPIRE (Use of a Multidrug Pill In Reducing Cardiovascular Events) trial suggest that a polypill combining antiplatelet and cholesterol- and blood pressure (BP)-lowering drugs is effective for improving adherence and reducing BP and low-density lipoprotein cholesterol (LDL-C) levels among patients with or at risk for cardiovascular disease (CVD).

Simon Thom, MD, presented data from UMPIRE, which randomized 2,004 subjects with established CVD or ≥15% 5-year CVD risk to treatment with a fixed-dose combination or usual care. Two fixed-dose combinations were used in the trial: one version combined aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg; the second version replaced atenolol with hydrochlorothiazide 12.5 mg. Primary outcomes included self-reported adherence to medication, and changes in systolic BP and LDL-C from baseline.

Adherence was significantly higher among patients who received the fixed-dose polypill: 86% vs 65% for usual care (*P*<0.0001). Systolic BP was significantly improved in patients receiving the polypill: 129.3 mm Hg vs 131.7 mm Hg for usual care (*P*=0.0005).

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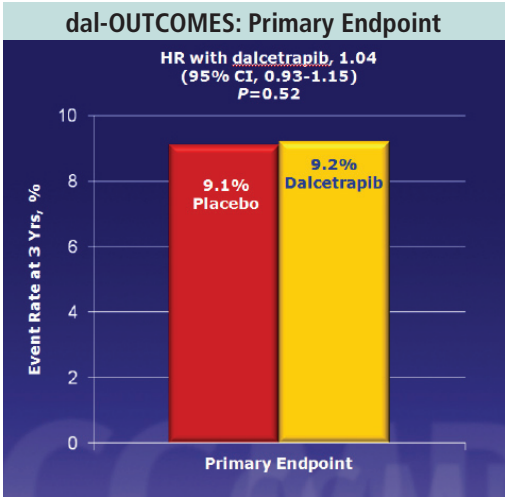
dal-OUTCOMES CONTINUED FROM PAGE 1



Dalcetrapib increased levels of high-density lipoprotein cholesterol (HDL-C) by 31% to 40% from baseline compared with reductions of 4% to 11% for placebo. A limited effect on low-density lipoprotein cholesterol (LDL-C) was noted for dalcetrapib.

No significant association between baseline HDL-C and cardiovascular risk was seen in either treatment group. Explaining this lack of association, Dr Schwartz noted that when patients are treated with risk-reducing drugs, HDL-C may no longer be a risk factor. Patients in the dal-OUTCOMES population were also taking background statins (97%); aspirin (97%); clopidogrel, ticlopidine, or prasugrel (89%); beta blockers (88%); and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (79%). Moreover, revascularization for the index ACS event were implemented prior to randomization in 91% of the cohort.

Dalcetrapib was well tolerated over the course of the trial. However, mean systolic blood pressure was 0.6 mm Hg higher among patients taking dalcetrapib than placebo ($P<0.001$). Levels of high-sensitivity C-reactive protein (CRP) were 18% higher in the dalcetrapib group ($P<0.001$).

In a subsequent discussion, Alan Tall, MD, provided explanations for the failure of dalcetrapib in reducing cardiovascular risk. He suggested that moderate HDL elevation in patients who are optimally treated with statins and other agents has no impact on coronary heart disease, noting that other studies including JUPITER[1] (Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) demonstrated a lack of relationship of HDL concentration to clinical outcomes. Dr Tall also noted that CETP inhibition may produce a form of HDL that is dysfunctional, for example, in reverse cholesterol transport, adding that the benefits of raising HDL-C with dalcetrapib may have been outweighed by the modest but significant increase in systolic BP seen in the study. He said the clinical significance of the modest CRP increase is questionable, noting a similar increase seen in DEFINE[2] (Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib) with the CETP inhibitor, anacetrapib. Dr Tall concluded by suggesting that as a partial CETP inhibitor, dalcetrapib may have been insufficiently potent. High-level CETP inhibition or deficiency produces roughly 120% increases in HDL-C, as well as HDL particles that are qualitatively different. Ongoing phase III trials of potent CETP inhibitors—anacetrapib (REVEAL) and evacetrapib (ACCELERATE)—will evaluate whether CETP inhibitors reduce atherosclerotic CVD risk.

dal-OUTCOMEs is not the first trial involving CETP inhibitors to suffer early termination. In 2007, a phase III study of the first CETP inhibitor, torcetrapib*, was halted due to adverse cardiovascular events.

*Dalcetrapib is an investigational compound not approved for use by the US Food and Drug Administration.

References:

1. Ridker PM, Danielson E, Fonseca FA, et al; for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359(21):2195-2207.

2. Cannon CP, Shah S, Dansky HM, et al; for the DEFINE Investigators. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med.* 2010;363:2406-2415.

3. Barter PJ, Caulfield M, Eriksson M; for the ILLUMINATE Investigators. *N Engl J Med.* 2007;357:2109-2122.

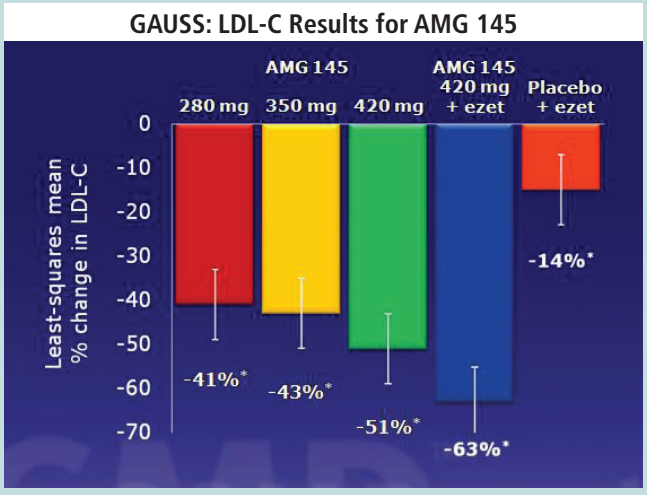
Schwartz GG, Olsson AG, Abt M, et al; for the dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012. DOI: 10.1056/NEJMoa12067967.

Novel PCSK9 Inhibitors Show Promise CONTINUED FROM PAGE 1

Patients receiving AMG 145 and ezetimibe demonstrated the most dramatic least-squares percent change in LDL-C: 63% vs 14% control ($P<0.001$). Maximal reduction in LDL-C was seen within 2 weeks of treatment initiation with AMG 145, with or without ezetimibe, and the effect was sustained throughout 12 weeks.

LDL-C goals of <100 mg/dL and <70 mg/dL were achieved in 54% and 18% of patients, respectively, in the AMG 145-alone groups; 90% and 62% in the AMG 145 plus ezetimibe group; and 7% and 0% in the placebo plus ezetimibe group. Improvements were also seen for other lipid parameters, including total cholesterol, non–HDL-C, apolipoprotein B, and ratios of total cholesterol to HDL-C and apo B/apo A1. Notably, lipoprotein(a) levels were reduced by 20% to 26% with AMG 145 plus ezetimibe.

Myalgia was the most common side effect reported among AMG 145-treated patients. At baseline, participants' mean age was



Ezet=ezetimibe
*$P<0.001$ vs placebo + ezetemibe

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Novel PCSK9 Inhibitors Show Promise CONTINUED FROM PAGE 3

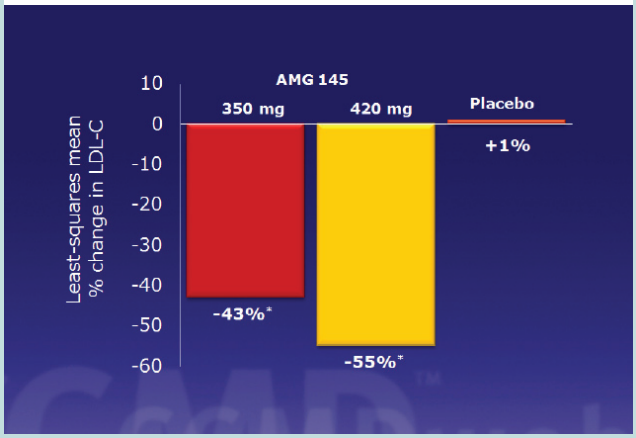
62 years, 64% were female, and mean LDL-C was 193 mg/dL; 50% of patients were high risk or moderately high risk based on National Cholesterol Education Program criteria.[2]

RUTHERFORD trial[3]

The Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) trial assessed two doses of AMG 145 for reducing LDL-C among patients with familial hypercholesterolemia.

This phase II, multicenter, double-blind, randomized, placebo-controlled, dose-ranging study enrolled 168 patients with LDL-C ≥100 mg/dL and TG ≤400 mg/dL despite ≥4 weeks of stable statin or other lipid-lowering therapy. Patients were randomized to AMG 145 350 mg or 420 mg, or to placebo subcutaneously every 4 weeks. The primary endpoint was percent change from baseline LDL-C at Week 12.

RUTHERFORD: LDL-C Results for AMG 145



*P<0.001 vs placebo

Frederick Raal, MD, presented results demonstrating that AMG 145 in doses of 350 mg and 420 mg reduced LDL-C by 43% and 55%, respectively, compared with a 1% increase seen with placebo (P<0.001). Treatment with AMG 145 420 mg and 350 mg resulted in 89% and 70% of patients achieving LDL-C<100 mg/dL, and 65% and 44% of patients achieving LDL-C <70 mg/dL, respectively, compared with 2% and 0% receiving placebo, respectively. The study doses of AMG 145 induced significant changes in other lipid parameters.

No clinically significant adverse effects of treatment were noted. Patients' baseline characteristics: 47% female; 89% white; mean age, 50 years; mean LDL-C, 156 mg/dL; 21% of patients had existing coronary artery disease; 90% of patients were on intensive statin therapy, often in combination with ezetimibe (64%).

RN316 for primary hypercholesterolemia

In two phase II trials, the novel PCSK9 inhibitor, RN316, was assessed for efficacy, safety, and tolerability for LDL-C lowering when added on to high-to-maximal doses of statins among subjects with primary hypercholesterolemia.

Barry Gumbiner, MD, presented composite data from two studies in which RN316 was administered intravenously at 0.25, 1.0, 3.0, and 6.0 mg/kg every four weeks. These doses were compared against placebo. After 12 weeks, significant reductions were seen in LDL-C, and total cholesterol was reduced and HDL-C increased in the 3.0- and 6.0-mg/kg doses. No significant changes were observed for TG. Adverse events were similar in the active treatment and placebo groups; myalgia risk appeared to be low, although elevations in creatine kinase were reported.

Discussing these trials of PCSK9, Peter W. Wilson, MD, noted that AMG 145 and RN316 were effective for lowering LDL-C, non–HDL-C, and apolipoprotein B, adding that the lipid effects of these agents are additive to other LDL-C lowering therapy.

*AMG 145 and RN316 are investigational compounds not approved for use by the US Food and Drug Administration.

The Science Behind PCSK9 Inhibitors

PCSK9 is a protein that binds to LDL receptors and prevents them from recycling. As a result, PCSK9 reduces the liver's ability to remove LDL-C from the blood, causing high levels in the serum.

PCSK9 inhibitors are manmade monoclonal antibodies that are designed to bind PCSK9, thereby decreasing circulating levels of LDL-C.

References:

1. Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin –intolerant patients. The GAUSS randomized trial. *JAMA*. 2012;308(23):doi:10.1001/jama.2012.25790.

2. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-2497.

3. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia. The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) Randomized Trial. *Circulation*. 2012;126:2408-2417.

UMPIRE Calls PolyPill Effective CONTINUED FROM PAGE 2

Similarly, LDL-C levels were also significantly improved with the polypill: 84.3 mg/dL (2.18 mmol/L) vs 88.5 mg/dL (2.29 mmol/L) for usual care (*P*=0.0005). (*See figure for treatment effects.*) Improvements were sustained throughout the 15-month trial duration.

	Fixed-dose combination (n=1,002)	Usual care (n=1,002)	Treatment effect (95% CI)	*P*
Adherence, %	86%	65%	1.33 (1.26-1.41)	<0.0001
Systolic BP, mm Hg	129.3	131.7	-2.6 (-4.0 to -1.1)	0.0005
LDL-C, mg/dL	84.3	88.5	-0.11 (-0.17 to -0.05)	0.0005

At baseline, 88% of patients in each treatment arm had established CVD, and 28% had diabetes. Mean age was 62 years; 81.5% of participants were male. Median systolic BP was 137 mm Hg.

In subsequent discussion, Andrew M. Tonkin, DEPM, said that the trial established the case for polypill use in the CVD setting.

CABG Trumps DES-PCI for Diabetes

Coronary artery bypass grafting (CABG) surgery was more effective than percutaneous coronary angiography (PCI) using drug-eluting stents (DES) for patients with diabetes who have multivessel coronary artery disease (CAD), according to data from the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial.

The trial randomly assigned 1,900 patients with diabetes and advanced CAD to undergo CABG or DES-PCI; patients were followed for a minimum of 2 years (mean, 4.37). The primary oucome was a composite of all-cause mortality, nonfatal myocardial infarction (MI), or nonfatal stroke.

The primary outcome occurred among 352 patients: 205 in the PCI group and 147 in the CABG group; the rate of the primary outcome was lower in the CABG group than in the PCI group (*P*=0.005). The event rate at 5 years was 26.6% for PCI and 18.7% for CABG, which translated into an absolute difference of 7.9%, driven by differences in rates of MI and all-cause mortality. Stroke occurred more frequently in the CABG group.

Reference:

Farkouh ME, Domanski M, Sleeper LA, et al; for the FREEDOM Trial Investigators. Strategies for Multivessel Revacularization in Patients with Diabetes. *N Engl J Med.* 2012. DOI: 10.1056/NEJMoa1211585.

Studies Assess Role of PUFA for Prevention of Atrial Fibrillation

Prevention of atrial fibrillation (AF) with polyunsaturated fatty acids (PUFA) was discussed in two clinical trials.

In the OPERA (Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation) trial, investigators found no difference in the primary endpoint, occurrence of postoperative AF of ≥30 seconds, between patients randomized to perioperative omega-3 supplementation or placebo: 30.0% vs 30.7%, respectively (odds ratio, 0.96; 95% CI, 0.77-1.20; *P*=0.74). No significant differences were seen for secondary endpoints, including sustained, symptomatic or treated postoperative AF, postoperative AF excluding atrial flutter, total number of days with any postoperative AF, and proportion of days free of postoperative AF.

OPERA was a double-blind, placebo-controlled, randomized trial of 1,516 patients scheduled for cardiac surgery. Patients were randomized to omega-3 (1-g capsules containing ≥840 mg omega-3-PUFAs as ethyl esters) or placebo, with perioperative loading of 10 g over 3 to 5 days or 8 g over 2 days, followed postoperatively by 2 g/d until hospital discharge or postoperative day 10.

In the FORWARD (Fish Oil Research with Omega-3 for Atrial Fibrillation Recurrence Delay) trial, PUFA did not prevent the recurrence of AF among patients with previous AF. Patients who received PUFA had similar incidence of recurrent AF compared with those receiving placebo. Mortality, hospitalization rates, and AF-free survival (hazard rate for AF-free survival: 1.28; 95% CI, 0.77-1.89; *P*=0.171) were also similar between the two groups.

FORWARD was terminated prematurely due to the certainty of negative results.

Coming Soon: Expert Commentary on these data from CCMD Education Council Co-chair Robert Eckel, MD