EDITORIAL COMMENT

Therapy and clinical trials

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The year 2011 has thus far been dominated by the vigorous pursuit of interventions for patients with low levels of high-density lipoprotein cholesterol (HDL-C) and proatherogenic lipid profiles. The major setback of the early stoppage of the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial by the National Heart, Lung, and Blood Institute (NHLBI) [1] was seemingly offset by the demonstrated safety of the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib in the dal-VESSEL trial [2].

AIM-HIGH was a large (3414 patient), randomized, placebo-controlled study designed to assess the efficacy of high-dose, extended-release niacin in patients already receiving statins and at target low-density lipoprotein cholesterol (LDL-C) levels, but with either low HDL-C or elevated triglycerides. The study enrolled high-risk patients including 92% with established coronary heart disease (CHD), 52% with prior myocardial infarctions, 71% hypertensive individuals and 34% diabetic individuals [3]. The study was stopped on 25 April 2011, 18 months earlier than planned due to the lack of reduction in cardiovascular events (5.8 and 5.6% annual event rates for drug and placebo, respectively, over 32 months). Of greater concern was an increase in ischemic stroke with treatment (1.6 compared with 0.7% with placebo, $P = 0.02$), although nine of the 28 strokes in the niacin arm occurred at least 2 months (and up to 4 years) after discontinuation of therapy. The disappointing results were surprising and contrary to many prior smaller studies [4]. Mechanistically, the lipid benefits of niacin could have been offset by the negative glycemic impact and the medications necessary for its control in this diabetic/prediabetic cohort [5,6]. Although firm recommendations on the role of niacin in patients already receiving statins await the results of another large study, the Heart Protection Study 2 of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE) [7], these findings suggest a lesser role for adding extended release niacin to a statin when LDL-C is at target. Add-on niacin may still be beneficial when LDL-C is not at target [8]. AIM-HIGH results should also not dissuade niacin use in patients not taking statins (such as those intolerant to statins) in which benefit appears to be considerable [9•].

Coming after the ill-fated investigation of lipid level management to understand its impact in atherosclerotic events (ILLUMINATE) trial, which demonstrated increased cardiovascular events in patients receiving torcetrapib [10], dal-VESSEL randomized 476 patients with CHD or CHD risk factors to dalcetrapib 600 mg or placebo for 36 weeks with endpoints of cardiovascular safety, endothelial function (using brachial artery flow-mediated vasodilatation) and blood pressure [11]. Dalcetrapib, the least potent of CETP inhibitors, was previously shown to decrease CETP activity by 26–58% and increase HDL-C by 23–34% [12••]. In dal-VESSEL, dalcetrapib increased HDL-C by 31% and had no adverse effect on SBP, endothelial function or cardiovascular events [2]. The lack of negative impact on endothelial function further distinguishes dalcetrapib from torcetrapib, which induced endothelial dysfunction independently from CETP effects [13•]. The potential addition of dalcetrapib to our pharmacologic armamentarium, however, still awaits the results of the 15 600 patient dal-Outcome trial [14].

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Conflicts of interest

Dr Krasuski is on the speaker's bureaus of Actelion Pharmaceuticals and Roche Pharmaceuticals; a consultant for Actelion and on the scientific advisory board for Ventripoint. Dr ElMallah has no conflicts.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol Rationale and study design. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH). Am Heart J 2011; 161:471–477.

2 Luscher TF, Kastelein JJ, Duivenvoorden R, *et al.* Efficacy and safety of dalcetrapib in patients with or at risk of coronary heart disease: the dal-VESSEL trial [abstract 411]. In: European Society of Cardiology Congress; 2011; Paris, France.

3 AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial. Am Heart J 2011; 161:538–543.

0957-9672 DOI:10.1097/MOL.0b013e32834d208d

4 Services USDoHH. NIH stops clinical trial on combination cholesterol treatment, lack of efficacy in reducing cardiovascular events prompts decision. National Institute of Health News, U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute (NHLBI). 2011.

5 McKenney J, Bays H, Koren M, *et al.* Safety of extended-release niacin/laropiprant in patients with dyslipidemia. J Clin Lipidol 2010; 4:105–112.

6 Fazio S, Guyton JR, Lin J, *et al.* Long-term efficacy and safety of ezetimibe/simvastatin coadministered with extended-release niacin in hyperlipidaemic patients with diabetes or metabolic syndrome. Diabetes Obes Metab 2010; 12:983–993.

7 Armitage J, Baigent C, Chen Z, Landray M. Treatment of HDL to reduce the incidence of vascular events HPS2-THRIVE. 2007. clinicaltrials.gov.

8 Lyseng-Williamson KA. Niacin extended release (ER)/simvastatin (Simcor): a guide to its use in lipid regulation. Drugs R D 2010; 10:253–260.

9 • Devendra GP, Whitney EJ, Krasuski RA. Impact of increases in high-density lipoprotein cholesterol on cardiovascular outcomes during the Armed Forces Regression Study. J Cardiovasc Pharmacol Ther 2010; 15:380–383.

In this analysis of the Armed Forces Regression Study, which compared combination therapy with niacin and gemfibrozil to placebos in nonstatin-treated patients, patients were stratified into three groups: no HDL-C increase, mild HDL-C increase and large HDL-C increase based on their percentage of change in HDL-C over the first year of treatment. A progressively lower cardiovascular event rate was noted across these groups (30.4, 19.4 and 3.2%, respectively, $P < 0.01$), with an impact independent of changes in LDL-C. For every 1% increase in HDL-C, a 2% decrease in cardiovascular events was achieved, an impact similar to the previously reported epidemiologic impact of HDL-C.

10 Barter PJ, Caulfield M, Eriksson M, *et al.* Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007; 357:2109–2122.

11 Kastelein JJ, Duivenvoorden R, Deanfield J, *et al.* Rationale and design of dal-VESSEL: a study to assess the safety and efficacy of dalcetrapib on endothelial function using brachial artery flow-mediated vasodilatation. Curr Med Res Opin 2011; 27:141–150.

12 •• Stalenhoef AF, Davidson MH, Robinson JG, *et al.* Efficacy and safety of dalcetrapib in type 2 diabetes mellitus and/or metabolic syndrome patients, at high cardiovascular disease risk. Diabetes Obes Metab 2011. [Epub ahead of print]. doi: 10.1111/j.1463-1326.2011.01485.

The authors performed a meta-analysis of the five phase II trials that assessed the use of dalcetrapib in patients with type 2 diabetes mellitus and/or metabolic syndrome, low levels of HDL-C and high triglyceride levels. Analyses were performed for both 600 and 900 mg dosing of dalcetrapib for therapy durations of 4, 12 and 48 weeks. Dalcetrapib decreased CETP activity by 26–58% and increased HDL-C levels by 23–34%, depending on dose and duration of treatment. Dalcetrapib did not significantly affect LDL-C or apolipoprotein B levels, and no significant adverse effects were seen compared with placebo. This meta-analysis was early evidence of the safety of dalcetrapib, which was later confirmed in dal-VESSEL.

13 • Connelly MA, Parry TJ, Giardino EC, *et al.* Torcetrapib produces endothelial dysfunction independent of cholesteryl ester transfer protein inhibition. J Cardiovasc Pharmacol 2010; 55:459–468.

In this study, in-vivo endothelium-mediated vasodilation was assessed using ultrasound imaging of acetylcholine-induced changes in rabbit central ear artery diameter and compared torcetrapib to a structurally distinct CETP inhibitor (JNJ-28545595). Both drugs achieved similar degrees of CETP inhibition and HDL increase, but only torcetrapib induced hypertension and inhibited acetylcholine-induced vasodilation (endothelium-independent smooth muscle function remained unimpaired). The authors hypothesize that this was a major mechanism for the detrimental effects of torcetrapib on survival in the ILLUMINATE trial and conclude that this is torcetrapib-specific and unlikely to be a drug class effect.

14 Schwartz GG, Olsson AG, Ballantyne CM, *et al.* Rationale and design of the dal-OUTCOMES trial: efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome. Am Heart J 2009; 158:896–901; e893.

Further recommended reading

Marelli C, Gunnarsson C, Ross S, *et al.* Statins and risk of cancer: a retrospective •• cohort analysis of 45 857 matched pairs from an electronic medical records database of 11 million adult Americans. J Am Coll Cardiol 2011; 58:530–537.

A retrospective analysis of nearly 46 000 propensity-matched pairs of patients (on statin and off statin) who were followed for a mean of nearly 5 years. The incidence of cancer in patients taking statins was not different, 11.37 compared with 11.11%, hazard ratio 1.04 (95% confidence interval 0.99–1.09). Kaplan–Meier curves for diagnosis of any cancer also showed no difference over 10 years. There have previously been a number of studies suggesting either favorable or unfavorable effects of statins on various malignancies. This large study provided reassurance that statins are unlikely to significantly impact overall cancer risk.

Barter PJ, Rye KA, Tardif JC, *et al.* Effect of torcetrapib on glucose, insulin, and •• hemoglobin A1c in subjects in the investigation of lipid level management to understand its impact in atherosclerotic events (ILLUMINATE) trial. Circulation 2011; 124:555–562.

In this post-hoc analysis of ILLUMINATE trial, diabetic patients on a torcetrapib/atorvastatin combination compared with those on atorvastatin alone had lower plasma glucose and insulin levels ($P < 0.0001$ for both) at 3 months. By 6 months, the mean hemoglobin A1c level was 7.06% in the torcetrapib/atorvastatin arm compared with 7.29% in the atorvastatin arm ($P < 0.0001$). Torcetrapib also lowered glucose and insulin levels in patients without diabetes, although to a lesser degree. Although torcetrapib was plagued with problems that lead to its demise, it will be interesting to see if this favorable metabolic effect extends to other CETP inhibitors and how it can be harvested.

Roumie CL, Huizinga MM, Liu X, *et al.* The effect of incident antidiabetic regimens •• on lipid profiles in veterans with type 2 diabetes: a retrospective cohort. Pharmacoepidemiol Drug Saf 2011; 20:36–44.

A retrospective study of 17 774 patients in the Veteran's Administration system that compared time to initiation of lipid-lowering medication (LLM) and 12-month lipid profiles among new oral anti-diabetic (OAD) users. The median time to starting LLM was 2.35 years, not statistically different for users of sulfonylureas or combination OADs. Compared with metformin (MET) users, 12-month HDL-C was 1.35 mg/dl (95% CI −2.01, −0.72) lower and triglycerides were 5.7% higher (95% CI 1.5–10.0%) for sulfonylurea users and triglycerides were 24.8% (95% CI 0.7–54.5%) higher for thiazolidinedione users. The study suggests a delay in starting LLM in many diabetic patients, surprising given the wealth of evidence in this population, as well as the need to utilize MET as first-line therapy in these patients.

Karamanos B, Thanopoulou A, Drossinos V, *et al.* Study comparing the effect of • pioglitazone in combination with either metformin or sulphonylureas on lipid profile and glycaemic control in patients with type 2 diabetes (ECLA). Curr Med Res Opin 2011; 27:303–313.

A prospective 12-month trial that compared three different medical regimens in type 2 diabetic patients: pioglitazone (PIO) with MET, PIO with sulphonylurea and MET with sulphonylurea. After 12 months PIO with sulphonylurea and PIO with MET groups demonstrated greater increases in HDL-C compared with sulphonylurea with MET (8.3 and 9.2 versus 4.3%, respectively, $P < 0.001$), as well as greater decreases in hemoglobin A1c (1.53 and 1.46 versus 0.97%, respectively, $P < 0.001$ for both), triglycerides (20.7 and 21.5 versus 15.2%, respectively, $P < 0.001$) and LDL-C (15.2 and 14.6 versus 11.3%, respectively, $P < 0.001$ and $P < 0.01$, respectively). The analysis suggests a considerable lipid benefit for the addition of pioglitzone when MET and lifestyle modification fails to adequately control diabetes.