

Therapy and clinical trials

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Early 2010 was notable for the publication of two studies examining adjunctive therapy to statins in patients at high cardiovascular risk. Despite significant risk reduction with statins, evidence suggests considerable, residual cardiovascular risk in statin-treated patients [1–3]. In light of this, investigators of both the Action to Control Cardiovascular Risk in Diabetes Lipid Trial (ACCORD Lipid) [4^{**}] and the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: HDL and LDL Treatment Strategies in Atherosclerosis study (ARBITER 6-HALTS) [5^{**}] explored the efficacy of add-on therapy.

In ACCORD Lipid, 5518 high-risk diabetic patients receiving open label simvastatin were randomized to either placebo or masked fenofibrate and monitored for the primary outcome of major fatal or nonfatal cardiovascular events. After mean follow-up of 4.7 years, there were 291 events (2.2%) with fibrate compared to 310 events (2.4%) with placebo, a hazard ratio of 0.92 (0.19–1.08, $P=0.32$). Additionally, there were no statistically significant differences among secondary outcomes.

The ARBITER 6-HALTS study compared the effects of open label niacin/statin and ezetimibe/statin combinations on atherosclerotic progression in a population of patients with established coronary disease or the equivalent. The study was originally stopped after planned interim analysis showed niacin to be superior to ezetimibe with regard to the primary end point of change in carotid intimal medial thickness (CIMT) [6]. The most recent report includes an additional 107 patients who completed a mean treatment of 7 months and confirms that in this larger cohort ($n=315$), patients receiving niacin had significant regression in CIMT (-0.01 ± 0.003 , $P < 0.001$), whereas those receiving ezetimibe did not (-0.002 ± 0.002 , $P < 0.88$).

Although fibrates have well established cardiovascular benefits [7] and ezetimibe is known to beneficially modulate lipid parameters [8], the results of ACCORD Lipid

and ARBITER 6-Halts add to the growing body of literature suggesting limited utility of these agents in statin-treated patients. Polypharmacy is well known to increase the risk of adverse effects [9], and reducing statin dosage to accommodate one of these agents is currently not supported by evidence. In fact, recent analyses further strengthen the role of high-dose statins in such patients [10,11]. Unfortunately, statin adherence remains a significant obstacle to therapy, but one which could provide substantial benefit (including reduction of cardiovascular death) [12] if it could be overcome. Such support for statin monotherapy is important, particularly in light of recent studies suggesting the development of insulin resistance and even frank diabetes with statin use [13^{*},14^{*}].

Interestingly, ARBITER 6 showed atherosclerotic regression with the addition of niacin, suggesting that this old stalwart still has an important role to play in ameliorating the residual risk that statins do not address. Augmenting therapy with niacin should therefore be considered in patients at high cardiovascular risk who are already compliant with an intensive statin regimen. Clearly though, as we continue to investigate mechanisms to diminish cardiovascular risk, statins should remain the mainstay of any pharmacologic intervention.

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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 Baigent C, Keech A, Kearney PM, *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005; 366:1267–1278.
- 2 Colhoun HM, Betteridge DJ, Durrington PN, *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. *Lancet* 2004; 364:685–696.
- 3 Collins R, Armitage J, Parish S, *et al.* MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. *Lancet* 2003; 361:2005–2016.
- 4 Ginsberg HN, Elam MB, Lovato LC, *et al.* Effects of combination lipid therapy •• in type 2 diabetes mellitus. *N Engl J Med* 2010; 362:1563–1574. Type II diabetics receiving open label simvastatin were randomized to receive either fenofibrate or placebo and then monitored over a mean follow-up of 4.7 years for fatal or nonfatal cardiovascular events. The addition of fenofibrate was associated with a hazard ratio of 0.92 (0.19–1.08, $P=0.32$), and therefore was not associated with significant risk reduction. These findings do not support the addition of fibrates to statins to reduce cardiovascular risk in patients with diabetes.

- 5 Villines TC, Stanek EJ, Devine PJ, *et al.* The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis) final results and the impact of medication adherence, dose, and treatment duration. *J Am Coll Cardiol* 2010; 55:2721–2726.

Patients with coronary heart disease or an equivalent who were already on stable statin therapy were randomized to receive either ezetimibe or extended-release niacin. An additional 107 patients (7-month follow-up) were added to the original cohort (total $n = 315$, 14-month follow-up) and all were observed for changes in carotid intima media thickness. Those receiving the niacin/statin regimen had a significant regression in carotid IMT (-0.01 ± 0.003 , $P < 0.001$) over their baseline, whereas those receiving ezetimibe and a statin did not (-0.002 ± 0.002 , $P < 0.88$). These findings do not support the addition of ezetimibe to statins in the treatment of cardiovascular risk for patients with established coronary disease, but suggest that the addition of niacin is beneficial.

- 6 Taylor AJ, Villines TC, Stanek EJ, *et al.* Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 2009; 361:2113–2122.
- 7 Jun M, Foote C, Lv J, *et al.* Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 2010; 375:1875–1884.
- 8 Vasiliou GA, Konstantinos T, Anna IK, *et al.* Effectiveness of ezetimibe alone or in combination with twice a week atorvastatin (10 mg) for statin intolerant high-risk patients. *Am J Cardiol* 2008; 101:483–485.
- 9 Goumas GS. Is there evidence-based hypolipidemic treatment with clinical benefit beyond statins? *Angiology* 2009; 60:93–98.
- 10 Tikkanen MJ, Szarek M, Fayyad R, *et al.* Total cardiovascular disease burden: comparing intensive with moderate statin therapy insights from the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial. *J Am Coll Cardiol* 2009; 54:2353–2357.

- 11 Cannon CP, Steinberg BA, Murphy SA, *et al.* Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol* 2006; 48:438–445.

- 12 Shroufi A, Powles JW. Adherence and chemoprevention in major cardiovascular disease: a simulation study of the benefits of additional use of statins. *J Epidemiol Community Health* 2010; 64:109–113.

- 13 Koh KK, Quon MJ, Han SH, *et al.* Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. *J Am Coll Cardiol* 2010; 55:1209–1216.

A randomized, single-blind, placebo-controlled trial in which 44 patients received placebo and 42, 44, 43 and 40 patients received 10, 20, 40 and 80 mg of atorvastatin, respectively. A 2-month treatment period with atorvastatin was associated with both a significant elevation in insulin ($P < 0.05$, $P = 0.009$) and glycated hemoglobin ($P < 0.05$, $P = 0.008$) when compared to baseline or placebo. Furthermore the treatment groups experienced decreased insulin sensitivity compared to baseline (for each dose: $P = 0.312$, $P = 0.08$, $P < 0.001$ and $P = 0.008$, respectively) or compared to placebo ($P = 0.033$). These findings suggest that atorvastatin increases the risk of insulin resistance and potentially diabetes in the hypercholesterolemic patient.

- 14 Sattar N, Preiss D, Murray HM, *et al.* Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; 375:735–742.

In order to further investigate recent data on the risk of diabetes with statin therapy the authors of this meta-analysis combined data from 13 statin trials over the last 15 years. In 91 140 total participants, statin therapy was associated with a 9% increased incidence of diabetes (odds ratio 1.09, 1.02–1.17). This analysis suggests that statin therapy is associated with a small increase in the risk of diabetes; however, the risk is not significant enough to offset the known cardioprotective effects of this drug class.