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Therapy and clinical trials: management of diabetic dyslipidemia

Ishwarlal Jialal^a and Mandeep Bajaj^b

^a *Laboratory for Atherosclerosis and Metabolic Research, University of California Davis Medical Center, Sacramento, California*

^b *Baylor College of Medicine, Houston, Texas, USA*

Dyslipidemia commonly associated with type II diabetes includes elevated triglycerides, low levels of HDL-C, and preponderance of small dense LDL particles, with LDL cholesterol generally being similar to that of nondiabetic patients. The cornerstone of treatment for diabetic dyslipidemia is therapeutic lifestyle change. In addition to these measures, recent clinical trials have demonstrated the benefits of statin therapy. Therapy with 3-hydroxy-3-methylglutaryl (HMG) Co-reductase inhibitor (statins) in both the Heart Protection Study (HPS) [1] and the Collaborative Atorvastatin Diabetes Study (CARDS) [2] has shown that there is clear reduction in cardiovascular events in type 2 diabetes [1,2]. A recent meta-analysis of 18 686 diabetic patients (predominantly T2DM) from 14 randomized statin therapy trials showed that, for every mmol/l reduction in LDL-C, there was a 21% reduction in major vascular events and 13% reduction in vascular mortality with no effect on non-vascular mortality [3•]. It is important to realize that there is much residual risk that has to be targeted. Karalis [4•] in his review makes the recommendation that, in addition to statin therapy, the combination of lipid-lowering therapy to manage residual cardiovascular risk should include a fibrate and niacin. The author's major focus appears to be on the niacin therapy in diabetes. This is based largely on the benefits previously seen on niacin–statin combination in the HDL-Atherosclerosis Treatment Study (HATS) [5] and also the recently published Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 3 (ARBITER 3) [6•] study that showed that niacin–statin therapy vs. statin therapy alone resulted in greater reduction in carotid intima-media thickness (CIMT) and this included patients with coronary heart disease (CHD), type II diabetes, and metabolic syndrome. This strategy of combining niacin–statin therapy to optimize the lipid profile, that is, reducing the triglycerides to levels below 1.7 mmol/l (<150 mg/dl) and levels of non-HDL-C to below 3.4 mmol/l (<130 mg/dl) is not an unreasonable strategy for type II diabetes. However, niacin therapy should be instituted only in well controlled diabetic patients, and glycemic control should be monitored. Thus, in a diabetic patient without CHD, the recommendation is to achieve an LDL-C level below 2.6 mmol/l (<100 mg/dl), and in a patient with diabetes and CHD, the goal is to achieve an LDL-C level below 1.8 mmol/l (<70 mg/dl). In both of these groups, the level of non-HDL-C that embraces LDL, IDL, VLDL, and Lp(a) should be less than 3.4 mmol/l (130 mg/dl) and less than 2.6 mmol/l (100 mg/dl), respectively. In addition, it is desirable in diabetic patients to keep the triglyceride levels according to the American Diabetes Association (ADA) to below 1.7 mmol/l (<150 mg/dl) and to achieve levels of HDL at 1.0 mmol/l (>40 mg/dl) and at more than 1.3 mmol/l (>50 mg/dl) for men and women. Clearly, these additional goals could possibly be achieved with niacin–statin combination therapy; however, it should be emphasized in the diabetic population that there is no strong evidence base to back the benefit of niacin–statin therapy compared with statin therapy alone with regards to further prevention of cardiovascular events.

Correspondence to Dr Ishwarlal Jialal, Laboratory for Atherosclerosis and Metabolic Research, University of California Davis Medical Center, 4635 2nd Avenue, Research 1 Building, Room 3000, Sacramento, CA 95817, USA; Tel: +1 916 734 6590; fax: +1 916 734 6593; e-mail: ishwarlal.jialal@ucdmc.ucdavis.edu.

In the article by Steinmertz [7•], the author emphasized once again the benefits of statin therapy in HPS and CARDS studies. The author also points out that in other studies (Atherosclerosis, Atorvastatin Study for Prevention of Coronary Heart Disease end points in noninsulin-dependent diabetes mellitus (ASPEN) [8] and the German Diabetes and Dialysis Study (4D) [9]), statins have not been shown to have benefits in patients with type II diabetes;. In ASPEN, in 2410 type 2 diabetic patients, there was no benefit of statin therapy on the primary and secondary end points. Steinmertz also emphasizes the residual risks with statin therapy in patients with type 2 diabetes and goes on to make a strong case for fibrate therapy. The Fenofibrate Intervention and Even Lowering in Diabetes (FIELD) study evaluated the effect of treatment with fenofibrate 200 mg/day in reducing macrovascular and microvascular complications in 9795 patients with early stage type 2 diabetes [10]. At the end of the 5-year follow-up period, treatment with fenofibrate was associated with a nonsignificant 11% reduction in relative risk of the primary end point. There was, however, a statistically significant 11% relative reduction in risk for the secondary end point of total cardiovascular events, excluding unstable angina, and this was largely driven by significant reduction in risk for nonfatal myocardial infarction (MI) and coronary and all revascularization procedures. Interestingly, in the FIELD study, fenofibrate significantly decreased the need for retinal laser therapy by 30% and significantly reduced the evolution of albuminuria. On the basis of these lines of data, Steinmertz [7•] argues that, given the large residual risk, especially, as statins do not target HDL-C or triglycerides or both substantially, considerations should be given to the combination of statin–fenofibrate therapy, given the safety of this combination and added benefit of fenofibrate with regards to the progression of microvascular diabetes-related complications. Once again, while this is a viable strategy, that is, the combination of statin–fenofibrate in attempting to normalize the lipid profile, including the LDL, non-HDL, HDL, and the triglycerides, it needs to be emphasized there is no large evidence base to support this recommendation. We must await the results of the ongoing lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.

Both authors fail to comment on the recently published Glucose-Lowering Effect of WelChol study (GLOWS) study in which Zieve *et al.* [11••] show that colesevelam therapy in a randomized double-blind placebo control study resulted in a significant concomitant reduction in both LDL-C and hemoglobin A1c in type II diabetes. This makes colesevelam an attractive second-line therapy in diabetic patients.

Thus, it would appear at this juncture with regards to residual risk and optimizing the lipid profile in patients with type II diabetes that, in addition to targeting the LDL-C, there is a potential benefit in further raising the HDL-C level and lowering triglyceride-rich particles (non-HDL-C). Thus, it might be prudent at this point to aspire to achieve a LDL-C level below 2.6 mmol/l (<100 mg/dl) and non-HDL-C level below 3.4 mmol/l (<130 mg/dl) in all diabetic patients without CHD. Furthermore, there is a recent recommendation suggesting that Apo-B level will also be a target for treatment, given this superiority to LDL-C in predicting cardiovascular events [12•].

Thus, in high-risk patients, including diabetic patients, in addition to LDL level below 2.6 mmol/l (<100 mg/dl) and non-HDL level below 3.4 mmol/l (<130 mg/dl), it might not be unreasonable to aspire to an Apo-B level below 0.9 g/l (<90 mg/dl). In a diabetic patient with CHD, the goals would be LDL level below 1.8 mmol/l (<70 mg/dl), non-HDL level below 2.6 mmol/l (<100 mg/dl), and Apo-B level below 0.8 g/l (<80 mg/dl).

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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

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- 3••. Cholesterol Treatment Trialist' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18686 people with diabetes in 14 randomised trials of statins. *Lancet* 2008;371:117–125. [PubMed: 18191683] This is an excellent meta-analysis of 14 randomized trials including 18 686 patients with diabetes that clearly shows a significant reduction in all-cause mortality and cardiovascular mortality with statin therapy. The disappointment of this trial is that both the ASPEN and the German Diabetes and Dialysis Study were excluded from the analysis by the authors but discussed. It would have been interesting if both of these negative studies were included in the meta-analysis. It was also important to emphasize that 92% of the patients in these studies had type II diabetes.
- 4•. Karalis DG. The role of lipid-lowering therapy in preventing coronary heart disease in patients with type 2 diabetes. *Clin Cardiol* 2008;31:241–248. [PubMed: 17847038] This is a nice up-to-date review on the importance of initiating statin therapy based on the large clinical trials in patients with diabetes. Furthermore, the author suggests that serious consideration should be given to niacin–statin therapy in patients with diabetes.
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- 6••. Taylor AJ, Lee HJ, Sullenberger LE. The effect of 24 mo of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr Med Res Opin* 2006;22:2243–2250. [PubMed: 17076985] In this important study using carotid intima-media thickness, Taylor and his colleague's show that over a 2-year period there was a significant reduction in carotid intima-media thickness with a combination of extended release Niacin–statin therapy compared to statin therapy alone.
- 7•. Steinmertz A. Lipid-lowering therapy in patients with type 2 diabetes: the case for early intervention. *Diabetes Metab Res Rev* 2008;24:286–293. [PubMed: 18273835] In this study the author does an excellent review on the statin trials in diabetic patients including the negative trials; furthermore, for residual risk, he makes a strong rationale based on the benefit in the FIELD study on both a secondary end point and on microvascular complications that fenofibrate therapy should be considered in addition to statin therapy in optimizing the lipid profile and reducing residual risk in type II diabetes.
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- 11••. Zieve FJ, Kalin MF, Schwartz SL, et al. Results of the glucose-lowering effect of WelChol study (GLOWS): a randomized double-blind, placebo-controlled pilot study evaluating the effect of colestevam hydrochloride on glycemic control in subjects with type II diabetes. *Clin Ther*

2007;29:74–83. [PubMed: 17379048] This is the first study to clearly show that WelChol in a randomized, placebo-controlled trial significantly reduces plasma glucose, HbA_{1c}, and LDL-C in patients with type II diabetes on hypoglycemic agents.

- 12•. Bunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk. *J Am Coll Cardiol* 2008;51:1512–1524. [PubMed: 18402913] The recent guideline with regards to lipid management in patients with cardiometabolic risk brings into play the relevance of targeting both non-HDL-C and Apo-B levels in patients with increased cardiometabolic risk such as metabolic syndrome and type II diabetes.