No accord for the ACCORD-Lipid trial results

Glenn Matfin and Matthew Thorne

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Type 2 diabetes mellitus (T2DM) is a major risk factor for coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease (PAD). The prevalence of these macrovascular complications is increased three- to four-fold in T2DM, and is the cause of death in two-thirds of diabetes patients.

Multiple cardiovascular disease (CVD) risk factors are present in T2DM patients and include obesity, hypertension, hyperglycaemia, altered platelet function and prothrombotic state, pro-inflammatory state, and atherogenic dyslipidaemia (i.e. increased triglyceride [TG], decreased high-density lipoprotein [HDL] cholesterol, and increased small, dense low-density lipoprotein [sdLDL] cholesterol). The presence of these and other CVD risk factors in an individual is termed the metabolic syndrome.

Patients with established atherosclerotic CVD have a high risk of recurrent CV events. Accordingly, this patient group requires intensive CVD risk-factor modification. Increasing evidence supports considering T2DM to be a CHD risk equivalent. As a result, T2DM patients also require intensive CVD risk-factor modification (including smoking cessation support, control of hypertension, lipid lowering, glycaemic control, and antiplatelet agents), even in the absence of established atherosclerotic CVD.

Low-density lipoprotein (LDL) cholesterol lowering (especially with statin therapy) is effective in reducing CVD events in diabetes patients. However, recent epidemiological cross-sectional studies such as the Dyslipidemia International Study (DYSIS) [Leiter *et al.* 2009] have demonstrated a high level of lipid abnormalities in

statin-treated patients. In particular, in this study two-thirds to three-quarters of those with diabetes had LDL levels not at goal and/or elevated TG levels. The DYSIS results demonstrate a gap between accepted guidelines and clinical practice and the need for a more intensive and comprehensive lipid management in high-risk groups such as diabetes patients.

Although the relative reduction in CVD risk with statin therapy is typically 25–35% [Alsheikh-Ali *et al.* 2007], further LDL reduction with maximal doses of statin does not markedly reduce the residual risk [LaRosa *et al.* 2005; Cannon *et al.* 2004]. Various treatment guidelines appropriately identify LDL as the primary target for CVD prevention [National Institute for Health and Clinical Excellence, 2010; Ryden *et al.* 2007; Grundy *et al.* 2005], but also recognize that atherogenic dyslipidaemia is also a modifiable risk factor, and state that raising HDL and/or lowering TGs are worthwhile secondary targets. Various therapies are currently used to address atherogenic dyslipidaemia and include fibrates, niacin and omega-3 fatty acids (usually in addition to statin therapy) [Davidson *et al.* 2007; FIELD Study Investigators, 2005]. Of these various agents, niacin has the best evidence base (including CVD outcome data), but is limited by tolerability issues leading to poor patient adherence, whereas omega-3 fatty acids have the least clinical trial data. Fibrates (which are weak peroxisome proliferator-activated receptor [PPAR] α agonists) have beneficial effects on HDL, TGs, and have anti-inflammatory properties. Unfortunately, various fibrates that have been investigated in CVD outcome studies (primary and secondary prevention settings) have shown variable results.

Correspondence to:
**Glenn Matfin, MSc (Oxon),
MB ChB, FFPM, FACE,
FACP, FRCP**
Joslin Diabetes Center,
Harvard Medical School,
Boston, MA 02215, USA
and Division of
Endocrinology, New York
University School of
Medicine, New York,
NY, USA
[glenn.matfin@
joslin.harvard.edu](mailto:glenn.matfin@joslin.harvard.edu)

Matthew Thorne, PhD
SAGE Publications Ltd,
London, UK

The most convincing fibrate CVD outcome study result to date was from the secondary prevention trial, the Veteran Affairs High-Density Lipoprotein Trial (VA-HIT) [Robins *et al.* 2001]. In the 627 subjects with T2DM, there was 31% decrease in the major adverse cardiovascular events (MACE) of nonfatal myocardial infarction (MI), CHD death, and stroke in the gemfibrozil-treated group compared with placebo. The major concern regarding gemfibrozil use is the increased risk of myopathy when combined with statins. In comparison, fenofibrate has been shown to cause less myopathy when used concomitantly with statins compared with gemfibrozil. This makes fenofibrate a potentially attractive option when combination fibrate and statin treatment is considered. However, CVD outcome data with fenofibrate therapy has so far been very disappointing.

The Fenofibrate Intervention and Endpoint Lowering in Diabetes (FIELD) study randomized 7795 T2DM patients to either fenofibrate or placebo [FIELD Study Investigators, 2005]. The primary endpoint (CHD death and nonfatal MI) was reduced by 11% in the fenofibrate group, but this did not reach statistical significance ($p=0.16$). One of the major factors suggested for the negative outcome was the increased use of statins (statin 'drop-in') during the study.

Against this background, the ACCORD-Lipid study was designed to investigate whether combination therapy with fenofibrate plus a statin, as compared with statin monotherapy, would reduce the risk of CVD in high-risk patients with T2DM [Ginsberg *et al.* 2010]. As announced at the annual congress of the American College of Cardiology in 2010, the primary composite endpoint of nonfatal MI, nonfatal stroke, or CV-related death (i.e. similar to VA-HIT endpoint) again unfortunately showed no significant difference between the fenofibrate and placebo groups. However, this population of 5518 patients was broader than that recommended by current guidelines for fenofibrate treatment: more than 80% did not have sufficiently low HDL and elevated TG (i.e. baseline HDL 40 mg/dl [~ 1.0 mmol/l]; and TG 162 mg/dl [~ 1.8 mmol/l]) to warrant additional treatment (to conventional statin) according to current clinical practice. The trial established that the combination therapy did not significantly benefit any of the primary or secondary outcomes

in this broad population; however, in the 17% of the population with more severe atherogenic dyslipidaemia (i.e. baseline HDL 29.5 mg/dl [0.76 mmol/l]; and TG 284 mg/dl [3.21 mmol/l]) CV events were reduced from 17.3% (monotherapy) to 12.4% (combination therapy) over 4.7 years ($p=0.057$). This subgroup analysis showed similar findings to analyses performed for other negative fibrate CV outcome studies.

The microvascular complications of diabetes (neuropathy, retinopathy, and nephropathy) result in considerable morbidity and mortality. Glycaemic control, diabetes duration, hypertension, hyperlipidaemia, and smoking remain important risk factors for these complications (i.e. the risk factors for microvascular complications are similar to those for macrovascular complications and are consistent with features of the metabolic syndrome) [Greenstein *et al.* 2007]. Can agents which target some of these CVD risk factors prevent or benefit microvascular complications? For example, the FIELD study [FIELD Study Investigators, 2005] showed a significant beneficial effect of fenofibrate on microvascular risk, with a reduction in the progression of microalbuminuria, and in the development and progression of diabetic eye disease [Keech *et al.* 2007]. The results of the retinopathy substudy of ACCORD-Eye are expected soon.

Debate about the optimal management of the CV residual risk in T2DM patients continues. In particular, the effects of adding fenofibrate to statin therapy are unproven. It is hoped that ongoing CVD outcome studies with newer formulations of niacin combined with statins will prove to be both effective and well tolerated. Therapies targeting HDL are also actively being investigated. However, several of these new molecular entities (NMEs) have failed during late-stage clinical development (e.g. the cholesterol ester transfer protein [CETP] inhibitor, torcetrapib). Despite this, HDL-based therapies appear to be an exciting prospect for the future and could fill a large unmet medical need.

Conflict of interest statement

The authors have no conflict of interest to declare in connection with this article.

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