Recent Advances in the Treatment of Atherogenic Dyslipidemia in Type 2 Diabetes Mellitus

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Key Words

Residual vascular risk • Atherogenic dyslipidemia • Cholesterol • Triglycerides • Diabetes mellitus • Kidney disease • Microvascular complications

Abstract

Despite best treatment efforts reducing low-density lipoprotein cholesterol, a substantial number of type 2 diabetes mellitus patients still experience progression of cardiovascular risk. Even with intensification of statin therapy, a substantial residual cardiovascular risk remains and atherogenic dyslipidemia is an important driver of this so-called residual risk. Besides statin therapy, new strategies evaluate the role of intensive combination lipid treatment for the entire type 2 diabetic population. The results from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid trial suggest that there is a lipid-related modifiable component to cardiovascular residual risk in statin-treated type 2 diabetic patients, and that further research should address patients with triglycerides above 204 mg/dl and high-density lipoprotein cholesterol below 34 mg/dl. Based on their respective lipid-modifying activity, the combination of a fibrate and statin is a logical approach to improving achievement of lipid targets in statin-treated patients with a glomerular filtration rate of >60 ml/min/1.73 m² and with residual athero-

genic dyslipidemia. The link between dyslipidemia treatment and diabetic retinopathy, nephropathy and neuropathy is an emerging new field and microvascular complications are targets for new treatments.

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Introduction

Substantial progress in the prevention and treatment of cardiovascular disease (CVD) [1–10] is now seriously challenged by the impact of global epidemics of obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM) [11]. Among these people, identified as having a ‘coronary risk equivalent’ [3–6], diabetic kidney disease remains the leading cause of end-stage renal disease. Thirty percent of all persons with T2DM develop diabetic nephropathy. Recent data raise the prospect of a reversal in renal death and coronary heart disease mortality rates, especially in younger men and women (<55 years), as a result of treatment efforts [12, 13].

Current standards of care for primary and secondary CVD prevention emphasize the importance of multifactorial intervention to achieve recommended targets for low-density lipoprotein cholesterol (LDL-C) which are often not met [3–8]. In the STENO-2 study, intensive

multifactorial intervention significantly reduced cardiovascular events during a mean of 7.8 years of post-treatment follow-up [hazard ratio (HR) = 0.47, 95% CI = 0.24–0.73, $p = 0.008$] and cardiovascular mortality during a mean of 5.5 years (HR = 0.43, 95% CI = 0.19–0.94, $p = 0.04$), but failed to prevent the development or progression of microvascular disease in up to 50% of patients [14, 15].

Several studies indicate that significant CVD risk persists after treatment with statins [16–26]. Three recent meta-analyses of the Cholesterol Treatment Trialists' collaborators including 90,056 and 170,000 subjects (18,686 with diabetes) from 14 and 26 randomized trials reported that for each millimole per liter lowering of LDL-C, statin therapy was effective in reducing the risk for major vascular events by 21%. Despite this, the residual risk of major vascular events over a 5-year period remained at 14% of patients experiencing a cardiovascular event [27–29]. Achieving new targets of 70 mg/dl LDL-C patients are left with a high residual risk [30, 31].

In patients with T2DM, nephropathy and/or established CVD, atherogenic dyslipidemia, characterized by elevated triglycerides (TG) and a low plasma concentration of high-density lipoprotein cholesterol (HDL-C), often with elevated non-HDL-C, is prevalent [32–34]. About two thirds of statin-treated patients with coronary heart disease risk equivalents and well-controlled LDL-C levels have low HDL-C levels (<40 mg/dl in men and <50 mg/dl in women) [35]. Elevated TG (>150 mg/dl) is also common, affecting about 50% of adults with prior CVD [34]. The present review discusses treatment issues in patients with T2DM and early nephropathy with respect to atherogenic dyslipidemia and residual risk.

Macrovascular Risk and Atherogenic Dyslipidemia

Elevated TG and low HDL-C are predictors of CVD, independent of LDL-C. The PROCAM (Prospective Cardiovascular Münster) study assessed the non-LDL-C-related dyslipidemia risk of myocardial infarction (MI) in 823 men with a first MI as compared with 823 MI-free controls matched for sex, age, smoking, diabetes mellitus, blood pressure and LDL-C. Overall, the odds of MI in men with low HDL-C (<1.15 mmol/l) were 2.6 times those of men with high HDL-C (≥ 1.15 mmol/l), and the odds of MI in men with high TG (≥ 1.71 mmol/l) were 1.4 times those of men with lower TG. If LDL-C was <2.58 mmol/l, relative MI odds attributed to low HDL-C increased to 3.4, while relative odds attributed to high TG

increased to 2.6; men in this LDL category with low HDL-C and/or high TG displayed an MI odds ratio of 5.0. MI risk associated with low HDL-C and/or high TG is substantial, particularly if LDL-C is low [36].

In a recent meta-analysis of 29 prospective studies including 262,525 subjects of whom 10,158 were coronary heart disease cases, the odds ratio for coronary risk was 1.72 (95% CI = 1.56–1.90) when individuals in the highest TG tertile were compared with those in the lowest tertile of usual log-TG values (corresponding to >178 vs. <115 mg/dl), adjusted for major conventional cardiovascular risk factors including age, sex, smoking history, LDL-C and blood pressure [37].

Diabetic Microvascular Risk

Atherogenic dyslipidemia is also implicated in the pathogenesis of diabetic microvascular disease [38].

Nephropathy

Elevated levels of TG and TG-rich very-low-density lipoprotein also appear to be closely involved in driving the progression of albuminuria [39]. In the UKPDS, elevated TG levels were independently associated with incident microalbuminuria (HR = 1.13, 95% CI = 1.07–1.19, $p < 0.0001$) and macroalbuminuria (HR = 1.19, 95% CI = 1.11–1.27, $p < 0.0001$) [40]. These data add to other findings that hypertriglyceridemia was a predictive factor for the development and progression of renal complications [41] and the need for future renal replacement therapy [42, 43]. Individuals with diabetes and without nephropathy have higher HDL-C levels than those with nephropathy, suggesting that higher HDL-C levels may be protective against the development of albuminuria [44–46].

Retinopathy

A number of studies suggest that serum lipids may have a causative role in the development and progression of diabetic retinopathy, retinal exudates and diabetic maculopathy [47–49]. In the ETDRS (Early Treatment Diabetic Retinopathy Study), patients with higher baseline total and LDL-C and TG levels were at greater risk of developing maculopathy over the course of the study [47]. High TG levels were among the risk factors identified for proliferative diabetic retinopathy [50]. In the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) study, the severity of retinopathy was positively associated with TG and negatively associated with HDL-C [51].

Neuropathy

In the EURODIAB (European Diabetes) Prospective Complications study in T1DM patients, elevated TG together with higher levels of total and LDL-C and increased urinary albumin excretion rate were among the factors significantly associated with diabetic neuropathy [52]. In an additional report from the EURODIAB IDDM Complications study, lower HDL-C levels and elevated fasting TG levels were associated with autonomic neuropathy [53].

In conclusion, these data suggest that treatment of atherogenic dyslipidemia, in addition to current standards of care (control of LDL-C, glycemia, blood pressure), may represent another target to reduce the risk of developing diabetic microvascular complications. There is evidence that retinopathy may already be present in patients with impaired glucose tolerance but without clinically overt diabetes [54].

Intervention Studies Reducing Microvascular Outcomes

Diabetic Nephropathy

A body of evidence supports the benefits of statin therapy in reducing the rate of decline in renal function. A meta-analysis of 27 studies involving 39,704 subjects showed that statin treatment significantly reduced the rate of decline in estimated glomerular filtration rate (eGFR = 1.22 ml/min/1.73 m² per year slower than with placebo, 95% CI = 0.44–2.00, $p = 0.002$), equivalent to approximately 76% reduction [55]. Evidence from large prospective studies suggests that statins may reduce the rate of kidney function loss in subjects with or at risk of CVD. In the HPS (Heart Protection Study), treatment with simvastatin (40 mg/day) was associated with a significantly smaller decline in eGFR in patients at high risk of CVD ($p = 0.0003$), and this effect was more marked among patients with diabetes [56]. The GREACE (Greek Atorvastatin and Coronary Heart Disease Evaluation) study also showed a modest improvement (12%) in kidney function over 4 years in 800 patients treated with atorvastatin, compared with a decrease by 4% in placebo patients [57]. Furthermore, combined analysis of three large prospective studies (WOSCOPS, CARE and LIPID) showed that treatment with pravastatin reduced the adjusted rate of renal function loss by 8% and the risk of renal failure. In patients with CKD stages 2 and 3 at baseline, pravastatin reduced the adjusted rate of renal function loss by about 34%, although the absolute reduction in rate of loss was

small [58]. The TNT (Treating to New Targets) study showed that statin-related improvement in eGFR was significantly greater in patients treated with atorvastatin 80 mg compared to 10 mg daily [59]. Experimental evidence suggests that statins may alter the renal response to dyslipidemia via effects on inflammatory responses and endothelial function [60].

Preliminary analysis of the SHARP (Study of Heart and Renal Protection) does not show a benefit of combination therapy of simvastatin/ezetimibe on progression of renal disease and incidence of end-stage renal disease.

Regarding proteinuria, analysis of 15 randomized trials including 1,384 patients that evaluated the change in proteinuria or albuminuria, stratified by baseline urinary protein excretion, showed that statin treatment reduced albuminuria by 47% (95% CI = 26–67) and 48% (95% CI = 25–71) in people with baseline albuminuria ≥ 300 and 30–299 mg/dl, respectively, but did not affect albuminuria when baseline levels were <30 mg/dl. However, the strength of these findings was limited by the quality, size or design of the studies included in the analysis [61].

The DAIS (Diabetes Atherosclerosis Intervention Study) ($n = 418$) reported attenuation of the worsening of albumin excretion in T2DM patients (8% with fenofibrate vs. 18% with placebo, $p < 0.05$), mainly due to reduced progression from normal albumin excretion to microalbuminuria ($p < 0.001$) [62].

More recently, the FIELD study provided statistically significant evidence that fenofibrate treatment led to reduction in the progression of albuminuria (14% less progression and 15% more regression of albuminuria with fenofibrate compared with placebo, $p = 0.002$), a pre-defined study endpoint [63]. It should be noted that treatment with fenofibrate was also associated with a significant, albeit reversible, increase in serum creatinine.

Diabetic Retinopathy

Evaluation of the effect of statin therapy on diabetic retinopathy has so far proved negative. In the CARDS (Collaborative Atorvastatin Diabetes Study), a primary prevention study in T2DM patients, there was no evidence of a significant benefit on the progression of diabetic retinopathy among patients treated with atorvastatin [64]. It should also be noted that in the STENO-2 study, retinopathy developed or progressed in 48% of patients treated with intensive multifactorial therapy (including optimal statin treatment) over a 7.8-year period [14]. Furthermore, data from a US nested case-control study in 6,441 male diabetic patients showed no significant difference in statin use among patients with or with-

out diabetic retinopathy (OR = 1.01; 95% CI = 0.64–1.59) [65].

Data from the FIELD study [66] show that fenofibrate had significant preventive effects on the development of diabetic retinopathy, reducing first laser treatment (a pre-defined tertiary endpoint) by 31% ($p = 0.0002$). In analyses in which confirmation of the requirement for laser therapy was independently verified, the FIELD study reported a significant benefit in reducing requirement for first laser therapy for both macular edema [reduction in relative risk (RR) by 31%, $p = 0.002$] and proliferative retinopathy (reduction in RR by 30%, $p = 0.015$). The benefit of treatment was enhanced in patients without prior retinopathy (reduction in RR for all laser events by 49%, $p = 0.002$, compared with 24%, $p = 0.01$, in patients with a history of retinopathy). These effects were broad-based and achieved rapidly (within 8 months of starting treatment) and increased during the study. Within the FIELD trial, a subset of patients ($n = 1,012$) also participated in the FIELD ophthalmology substudy, in which retinal photographs were assessed. Treatment with fenofibrate was associated with significant reduction by 34% ($p = 0.022$) in the composite endpoint of 2-step progression of retinopathy grade, development of clinically significant macular edema and need for laser treatment [66]. Notably, these effects were achieved despite an excess of add-in lipid-modifying therapy (predominantly statins) in the placebo arm. The mechanism(s) of these effects of fenofibrate does/do not seem to be related to lipid levels, as there were no differences in baseline lipid values between the group of patients who underwent laser therapy and the group who did not [66].

There are a number of limitations in the FIELD study [67], notably the absence of retinal photography at baseline in the main study to establish the extent of preexisting retinopathy, the lack of prospective specification of criteria defining the need for laser therapy, and the small number of events in both the main and substudy. Despite these limitations, the weight of evidence supports a beneficial role for fenofibrate treatment in preventing the development or progression of diabetic retinopathy in T2DM, especially among patients at the very early stages of this complication.

Diabetic Neuropathy

Experimental studies suggest beneficial effects of lipid-modifying treatment on neurovascular function and diabetic neuropathy [68, 69]. Preliminary observational data based on a longitudinal subgroup of 531 subjects with T2DM in the Freemantle Diabetes Study showed

that statin (HR = 0.65, 95% CI = 0.46–0.93) as well as fibrate (HR = 0.52, 95% CI = 0.27–0.98) were significantly inverse determinants of incident diabetic neuropathy ($p < 0.05$) [70]. Experimental evidence from a number of studies suggests that statin treatment may have a favorable effect on established diabetic neuropathy. In a mouse model of T2DM characterized by the development of severe peripheral neuropathy, treatment with rosuvastatin led to restoration of nerve vascularity and function to levels observed in nondiabetic mice. Limited clinical data also suggest that treatment with a statin (simvastatin) may have a beneficial effect in delaying the progression of early diabetic neuropathy, as assessed by the change in vibratory threshold measurements [71]. In the STENO-2 study, however, intensive multifactorial intervention (including widespread use of statin therapy) failed to prevent the development or progression of peripheral neuropathy in about 50% of patients [14].

A clinical study indicated that treatment with fish oil (EPA) at a dose of 1,800 mg/day for 48 weeks had beneficial effects on diabetic peripheral neuropathy and hemodynamics, as assessed by an increased cross-sectional area of the dorsalis pedis artery together with improvement in the perception of clinical symptoms and vibration perception threshold sense of the lower extremities [72]. The FIELD study showed that fenofibrate reduced the number of lower-extremity nontraumatic amputations (a prespecified tertiary outcome) compared with placebo (38%, $p = 0.011$) [73].

Therapeutic Approaches to Reducing Vascular Risk

Lifestyle modifications such as traditional Mediterranean diets, dietary sodium and exercise are cornerstones in the prevention and treatment of CVD, T2DM, the metabolic syndrome and most likely also in patients with incipient diabetic nephropathy. Data to support pharmacological intensification of blood glucose and blood pressure control are less than conclusive. In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) trial [74], intensive glycemic control versus conventional control reduced the incidence of combined microvascular and major macrovascular events by 10%, mainly due to a decrease in nephropathy (reduction in RR by 21%, $p = 0.01$). The ADVANCE trial also showed that intensive blood pressure lowering did not reduce the overall risk of microvascular events (reduction in RR by 9%, $p = 0.16$) [75]. Interim analysis of the ACCORD (Action to Control

Cardiovascular Risk in Diabetes) study showed that intensive glycemic control (lowering HbA_{1c} to a median of 6.4 vs. 7.5% with conventional control) increased mortality (by 22%, $p = 0.04$) after a mean of 3.5 years of follow-up [76].

While statins are effective in reducing non-HDL-C and apoB, effects on raising HDL-C and lowering TG tend to be less impressive and dependent on dose and lipid phenotype. While further reduction of LDL-C can be achieved with inhibitors of cholesterol absorption, such as ezetimibe, other lipid-modifying therapies are usually needed for treatment of higher TG concentrations and low HDL-C. Current treatment guidelines therefore recommend the addition of either a fibrate, niacin or omega-3 fatty acids to achieve non-HDL targets in patients with atherogenic dyslipidemia and at high risk of CVD [3–8].

Fibrates

Activation of PPAR- α by a fibrate has been shown to impact on all components of atherogenic dyslipidemia [77–80] (TG minus 30–50% depending on pretreatment levels; HDL-C increase by 5–15%) [81]. Fibrates can reduce the risk of major cardiovascular events predominantly by prevention of coronary events [82]. A pooled analysis of 18 fibrate trials providing data for 45,058 participants demonstrated a 10% RR reduction (95% CI = 0–18) for major cardiovascular events ($p = 0.048$) and a 13% RR reduction (95% CI = 7–19) for coronary events ($p < 0.0001$), but had no benefit on stroke or all-cause mortality. Fibrates reduced the risk of albuminuria progression by 14% (range 2–25; $p = 0.028$). Fibrate monotherapy is associated with a risk of myopathy [83–85]. This risk is enhanced during coadministration with statins, particularly at higher statin doses, or in renal failure. Fenofibrate treatment should be stopped when eGFR drops below 60 ml/min/1.73 m². In the recent meta-analysis, serious drug-related adverse events were not significantly increased by fibrates (17,413 participants, 225 events; RR = 1.21, 0.91–1.61; $p = 0.19$), although increases in serum creatinine concentrations were common (RR = 1.99, 1.46–2.70; $p < 0.0001$).

It is also worth noting that none of the 1,000 patients in the FIELD study who received both fenofibrate and a statin developed rhabdomyolysis during the mean 5-year follow-up. In the FIELD study, plasma creatinine remained on average 10–12 $\mu\text{mol/l}$ higher in the fenofibrate than in the placebo group (median concentration at study close 91 vs. 80 $\mu\text{mol/l}$ in the placebo group, $p < 0.001$). This effect was reversible within 8 weeks of stop-

ping study treatment, with levels returning to those exhibited in the placebo group [63] indicating that there was no impairment of renal function during the 5 years of fenofibrate treatment.

Niacin

Niacin is the most potent agent currently available for raising HDL-C (by about 20–25% with 1.5 g daily extended-release formulation) [86, 87]. Niacin also lowers LDL-C by about 10–15%, TG by about 15–25% and lipoprotein(a) by about 15–25% [86–90]. Niacin has numerous anti-atherothrombotic effects that improve endothelial function, reduce inflammation, increase plaque stability and diminish thrombosis. Niacin inhibits the coagulation cascade, decreases platelet aggregation and increases fibrinolytic activity, thereby accelerating and enhancing clot lysis. Flushing, the commonest side effect of niacin, is less problematic with extended-release niacin and even less – and less severe – in combination with laropiprant, an inhibitor of the prostaglandin D₂ receptor [91]. However, the long-term safety of laropiprant combined with niacin has yet to be established.

The ACCORD Lipid Trial

The ACCORD Lipid trial [92] randomized 5,518 high-risk T2DM patients at target for LDL-C (approx. 100 mg/dl or approx. 2.6 mmol/l at baseline decreasing to approx. 80 mg/dl or approx. 2.0 mmol/l on simvastatin, mean dose 22 mg/day) to fenofibrate or placebo. Fenofibrate treatment lowered TG by 22% from baseline versus 8.7% with simvastatin alone, and raised HDL-C by 8.4 versus 6.0% with simvastatin alone. The study failed to demonstrate a benefit for a composite of cardiovascular death, nonfatal MI or nonfatal stroke. Fenofibrate significantly reduced the incidence of both microalbuminuria ($p = 0.01$) and macroalbuminuria ($p = 0.03$) versus simvastatin alone [92]. Predefined subgroup analysis highlighted a group of patients with baseline TG levels ≥ 204 mg/dl (2.3 mmol/l) and HDL-C levels ≤ 34 mg/dl (0.88 mmol/l) who received simvastatin alone. This group suffered 70% more primary endpoints than those without this lipid profile (17.3 vs. 10.1%). Adding fenofibrate to simvastatin resulted in a 31% reduction in events (from 17.3 to 12.4%, absolute risk reduction 4.9%). The conclusion from the ACCORD Lipid trial is that the extension of fibrate treatment is not appropriate with respect to cardiovascular outcomes. Unlike statins, it appears that fibrates lower cardiovascular events mainly in patients who have abnor-

mal lipid levels at baseline, especially elevated TG and low levels of HDL-C (i.e., atherogenic dyslipidemia) [93–96]. A conservative estimate of the percentage of type 2 diabetes patients with atherogenic dyslipidemia (TG $\geq$ 204 mg/dl and HDL-C $\leq$ 34 mg/dl) is likely to be between 10 and 15%. The implication from the ACCORD Lipid trial is that not all patients with T2DM benefit from dyslipidemia management beyond LDL-C [92]. Combination treatment with fenofibrate-simvastatin was safe and well tolerated in the total study population, with no excess myopathy versus simvastatin monotherapy.

Conclusion

Improvements in CVD outcomes are now challenged by the impact of global epidemics of obesity, metabolic syndrome, and diabetes. Highlighting atherogenic dyslipidemia as a key modifiable factor contributing to residual macrovascular risk in statin-treated patients implicates this in the pathogenesis of microvascular residual risk in diabetes patients. Considering the evidence, the following

actions should be addressed: (a) increase the awareness of the extent and importance of residual vascular risk among the clinical community; (b) understand factors which contribute to the residual vascular risk remaining in dyslipidemic patients by research; (c) lifestyle modification is an important first step for reducing residual vascular risk; the strong potential of nutrition and exercise is not well appreciated and underutilized; (d) optimal therapeutic intervention aimed at achievement of all lipid targets with the addition of niacin or a fibrate, or possibly omega-3 fatty acids to optimal statin therapy; (e) earlier intervention in the natural history of atherosclerosis, with lifestyle therapy and drug treatment as appropriate, and (f) multifactorial intervention involving lifestyle modification, combination therapy targeting all lipid goals, and tight control of blood pressure and glycemia as the optimal approach to reducing residual vascular risk in dyslipidemic patients. A recent position paper from the Residual Risk Reduction Initiative addressed this relevant clinical issue [97]. Two major ongoing studies, AIM-HIGH and HPS2-THRIVE, will provide crucial information regarding the use of combination lipid-altering treatments in the future.

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