Treating Dyslipidemia in Type 2 Diabetes

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KEYWORDS

• Diabetes • Lipids • Cardiovascular risk • Clinical trials

KEY POINTS

- Atherosclerotic cardiovascular disease (ASCVD) presents an ongoing major public health challenge.
- There is an urgent need to identify and develop the most effective preventive strategies for reducing cardiovascular risk in patients with diabetes.
- Targeting dyslipidemia in patients with diabetes forms a cornerstone of approaches to cardiovascular prevention.

INTRODUCTION

Randomized controlled trials have demonstrated that lowering cholesterol and blood pressure has a beneficial effect on cardiovascular event rates in the primary and secondary prevention settings.[1–5] Although implementation of these therapies in clinical practice have contributed to reductions in attributed mortality, atherosclerotic cardiovascular disease (ASCVD) presents an ongoing major public health challenge. The global increase in obesity and diabetes are likely to underscore a considerable part of this challenge and associate with a greater risk of adverse outcomes in those patients whose ASCVD has become clinically manifest. Accordingly, there is an urgent need to identify and develop the most effective preventive strategies to reducing cardiovascular risk in patients with diabetes. Targeting dyslipidemia in these patients forms a cornerstone of approaches to cardiovascular prevention.

DYSLIPIDEMIA IN DIABETES

In association with insulin resistance, type 2 diabetes is typically accompanied by a specific lipid phenotype, characterized by elevated triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C) and the observation that low-density lipoprotein cholesterol (LDL-C) levels are often within the normal range.[6] Activity of lipoprotein lipase, a major factor implicated in the metabolism of triglyceride-rich lipoproteins, is impaired in the setting of hyperglycemia.[7,8] The resulting increase in circulating concentration of triglyceride-rich lipoproteins activates other lipid metabolism factors that tend to decrease HDL-C levels.[9] Many lines of evidence suggest that low-density lipoprotein (LDL) per se is not normal in most patients with diabetes.[10] However, elevated LDL-C levels are encountered in 25% of patients[11] and diabetes is typically accompanied by elevated levels of small, dense LDL particles.[12,13] Accordingly, in patients in whom LDL-C levels are considered to be

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normal, the LDL profile remains associated with increased atherogenicity.[14–18] Each of these findings presents considerable opportunity for targeting dyslipidemia, which can reduce cardiovascular risk in patients with type 2 diabetes.

STATINS AND DIABETES

Randomized controlled trials have consistently demonstrated that lowering LDL-C with statins reduces cardiovascular morbidity and mortality.[19,20] More recent studies comparing intensive and moderate statin therapy has supported the concept of benefits with more aggressive lipid lowering.[21–25] Within each of these studies, investigation of the subgroup of patients with diabetes has failed to demonstrate any evidence of heterogeneity, suggesting that statins afford a similar degree of clinical benefit in the setting of diabetes. This has been subsequently confirmed by pooled analyses of the statin trials.[3] The only placebo-controlled clinical trial performed exclusively in subjects with diabetes demonstrated a reduction in cardiovascular risk with atorvastatin.[26] These findings have underscored the consistent emphasis in treatment guidelines to assume that patients with diabetes should be considered to be at high cardiovascular risk and require treatment with a statin, regardless of the presence of clinically manifest ASCVD or baseline LDL-C levels.

In parallel, it has become apparent that statins, particularly when administered as intensive doses, are associated with a greater incidence of diagnoses of diabetes within those studies. Observations from Mendelian randomization show that polymorphisms are associated with low activity of either hydroxyl-methyl-glutaryl coenzyme A reductase[27] or proprotein convertase subtilisin kexin type 9 (PCSK9)[28] not only with low LDL-C levels but also with an elevated risk of diabetes. When combined with reports of a lower prevalence of diabetes in patients with familial hypercholesterolemia,[29] it would seem that the observation of new-onset diabetes in the statin trials is more likely a function of the lipid lowering than of the statin itself.[30,31] Nevertheless, given the cardiovascular benefits of statin therapy in patients with type 2 diabetes, these observations have not altered clinical practice in patients at high risk for ASCVD who require intensive lipid lowering with a statin.

ADDITIONAL LOW-DENSITY LIPOPROTEIN CHOLESTEROL-LOWERING AGENTS AND DIABETES

Ezetimibe is a cholesterol absorption inhibitor that reduces LDL-C by up to 20%.[32] In addition, it lowers the inflammatory marker C-reactive protein (CRP) when administered in combination with statins.[33] When added to simvastatin in patients with a recent acute coronary syndrome, ezetimibe produced a modest reduction in clinical events on long-term follow-up.[34] Subgroup analysis revealed that this clinical benefit was largely observed in patients with diabetes. Although this is likely to reflect a greater modifiability of risk in the presence of diabetes and acute coronary syndromes, it remains to be further characterized. The findings do suggest that patients with diabetes who experience an acute coronary syndrome should be treated intensively with the combination of statin and ezetimibe with a view to achieving an LDL-C less than 50 mg/dL.

PCSK9 plays an important role in regulating hepatic expression of the LDL receptor. Inhibitory monoclonal antibodies directed against circulating PCSK9 have been demonstrated to decrease LDL-C by up to 60% when administered as either monotherapy or in combination with statins.[20] Similar lipid effects have been reported in trials exclusively performed with subjects with diabetes.[35] Recent trials have demonstrated that treatment with evolocumab in addition to statins reduce LDL-C to less than 40 mg/dL and produce both regression of coronary atherosclerosis[36] and a reduction in cardiovascular events.[37] There is no evidence of heterogeneity in subgroup analysis, suggesting that patients with diabetes are likely to derive a clinical benefit from this therapy. Further analysis from the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial demonstrated higher placebo event rates in patients with diabetes and a greater absolute risk reduction with evolocumab, suggesting a lower number needed to treat.[38] Although there was no evidence in FOURIER of an increase in diagnoses of new-onset diabetes with evolocumab,[38] the Mendelian randomization data suggest that such an effect may ultimately be observed if a sufficiently high number of patients are treated for long enough.

Bempedoic acid is a liver-specific inhibitor of advanced treatment panel citrate lyase, which reduces hepatic cholesterol biosynthesis and upregulates LDL receptor expression in a similar fashion to statins. In contrast, the factor required for conversion of its prodrug to the active form is not present in skeletal muscle, underscoring its potential development for patients with statin intolerance. Lipid efficacy studies have demonstrated dose-dependent lowering of LDL-C by up to 30% and CRP by up to 40% in patients with and without diabetes.[39] A large clinical outcomes trial is currently evaluating the impact of bempedoic acid in patients with a high risk for