LDL Cholesterol Lowering in Type 2 Diabetes: What Is the Optimum Approach?

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Current estimates indicate that 21 million U.S. adults—roughly 10% of the adult population—have diabetes.[1] Owing in part to the growing epidemic of obesity in the United States, the prevalence of diabetes is expected to more than double to 48 million people by 2050.[2,3] Nearly 30 years ago, the Framingham Heart Study established that individuals with diabetes have a two to three times higher risk of cardiovascular events than nondiabetic people.[4] More recent studies have determined that diabetes is a coronary heart disease (CHD) risk equivalent based on findings that risk for coronary events in diabetic patients without previous CHD is equivalent to that of nondiabetic people with a history of CHD.[5,6] Heart disease mortality, however, is two to four times higher in patients with diabetes compared with those without diabetes.[1] The risk of death is particularly high in the early period after a CHD event. In the FINMONICA myocardial infarction (MI) register study, 28-day mortality after hospitalization for a first MI was nearly twofold higher in men with diabetes and almost threefold higher in women with diabetes compared with their nondiabetic counterparts.[7] In a recent analysis of pooled data from 11 trials of 62,036 patients with acute coronary syndromes conducted by the Thrombolysis in Myocardial Infarction Study Group, mortality at 30 days was significantly higher among diabetic than nondiabetic patients presenting with unstable angina/non–ST-segment elevation MI (2.1 vs. 1.1%; $P < 0.001$) and with ST-segment elevation MI (8.5 vs. 5.4%; $P < 0.001$).[8]

The U.K. Prospective Diabetes Study (UKPDS) established the importance of tight glycemic control in patients with diabetes.[9] Yet in isolation, control of hyperglycemia is not sufficient to decrease the high burden of cardiovascular disease (CVD) in this population.[10] Efforts to reduce cardiovascular morbidity and mortality in people with diabetes have therefore focused on overall or global risk factor management, including weight loss and increased physical activity, tight control of blood pressure and blood glucose, and intensive management of diabetic dyslipidemia.

IN BRIEF

Managing the high risk for cardiovascular morbidity and mortality in diabetic patients is a challenge for practicing clinicians. Reducing the burden of cardiovascular disease in diabetes should begin with assessment and treatment of elevated LDL cholesterol. Statins are the preferred treatment, and intensive statin therapy may be necessary to meet the current goal of < 100 mg/dl or the optional goal of < 70 mg/dl recommended for high-risk patients and to address other components of diabetic dyslipidemia. Along with aggressive glucose and blood pressure control, intensive treatment of LDL cholesterol in patients with diabetes can substantially affect long-term health outcomes.

The typical lipid disorder in patients with diabetes, diabetic dyslipidemia, is characterized by elevated triglycerides, low levels of HDL cholesterol, and increased numbers of small, dense LDL particles.[11,12]

The implementation of treatment goals for diabetes is challenging, however, and has been suboptimal in most clinical settings.[11] Data from the 1999–2000 National Health and Nutrition Examination Survey showed that only 37% of adults with diagnosed diabetes achieved a hemoglobin A_{1c} goal of < 7%, only 36% achieved a blood pressure goal of < 130/80 mmHg, and just 48% achieved a total cholesterol goal of < 200 mg/dl.[13] Moreover, only a very small minority (< 10%) of people with diabetes achieved all three treatment goals.[13] Achievement rates of LDL cholesterol goals are particularly poor among high-risk individuals with diabetes.[14,15] For example, in one recent survey, 40% of patients with both diabetes and CHD had LDL cholesterol levels greater than the goal of < 100 mg/dl recommended by the third National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines, and nearly 80% had levels above the optional goal of < 70 mg/dl.[15]

Although the difficulty of achieving aggressive LDL cholesterol goals in diabetic patients—many of whom are receiving multiple drug therapies and have concomitant medical problems—has often been cited as one factor contributing to poor control rates, a review of medical records of nearly 48,000 CHD patients both with and

without diabetes has shown that lipid management in general needs to be improved in patients with diagnosed diabetes. Despite overall increases in rates of lipid testing and treatment, patients with CHD and diabetes are still 26% less likely to have had a lipid profile and 17% less likely to receive lipid-lowering medication than are patients with CHD but without diabetes.[16]

As these data suggest, there are a number of ongoing opportunities to improve overall diabetes care. In particular, achievement of the intensive LDL cholesterol goals recommended by both the NCEP and the American Diabetes Association (ADA) has the potential to substantially improve long-term cardiovascular outcomes.[12,17] To this end, this review addresses three key issues related to lowering the risks associated with diabetic dyslipidemia: *1*) the substantial CHD risk associated with relatively normal LDL cholesterol; *2*) the value of lowering LDL cholesterol and normalizing atherogenic LDL particles in reducing cardiovascular risk; and *3*) the role of intensive statin therapy in achieving aggressive LDL cholesterol goals.

What Is Average LDL Cholesterol in Diabetes, and Why Is It a Concern?

Patients with diabetes frequently have lipid profiles that appear more benign than those of other high-risk people without diabetes. In general, LDL cholesterol levels in people with diabetes are not higher than those in people without diabetes who are matched for age, sex, and body weight.[12] In fact, the most common LDL cholesterol level in diabetes is "borderline high" (130–159 mg/dl).[12] Moreover, high LDL cholesterol levels (≥ 160 mg/dl) do not occur at higher-than-average rates in people with diabetes. Nonetheless, LDL cholesterol does not play less of a role in cardiovascular risk in people with type 2 diabetes. In fact, LDL cholesterol levels may underestimate cardiovascular risk in diabetes.[17] A large number of small, dense particles characterize the LDL fraction in diabetic individuals. These particles contain less cholesterol than normal-sized LDL particles, but they are exceptionally atherogenic.[10,18,19] Thus, levels of LDL may appear deceptively "normal" in cholesterol measurements.

Small, dense LDL particles are considered more atherogenic than the larger, buoyant LDL particles because they are more readily oxidized and glycated, which make them more likely to invade the arterial wall.[10,19] This can initiate atherosclerosis or lead to increased migration and apoptosis of vascular smooth muscle cells in existing atherosclerotic lesions.[10,19] As a consequence, elevated or "normal" LDL cholesterol may be more pathogenic in people with diabetes.

Beyond the importance of even modest elevations in LDL cholesterol in people with diabetes, it also appears that LDL cholesterol interacts with risk factors of the metabolic syndrome to magnify the risk of CVD.[10,12,20,21] The strong association between increased small, dense LDL particles and elevated triglycerides, for example, appears to be linked to the altered insulin sensitivity common in the metabolic syndrome and type 2 diabetes.[18,20] Insulin resistance in skeletal muscle promotes the conversion of energy from ingested carbohydrate into increased hepatic triglyceride synthesis, which in turn generates large numbers of atherogenic triglyceride-rich lipoprotein particles, such as very-low-density lipoprotein (VLDL).[20,22] As a further consequence, through the action

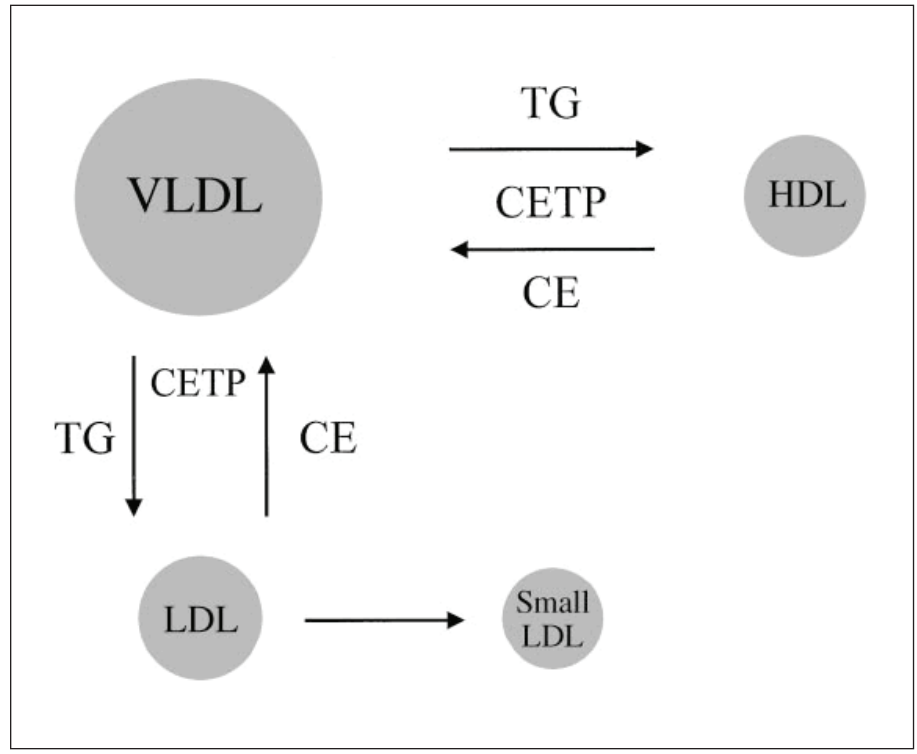

Figure 1. Plasma lipid exchange. In the presence of increased concentrations of VLDL in the circulation, cholesteryl ester transfer protein (CETP) will exchange VLDL triglyceride (TG) for cholesteryl ester (CE) in the core of LDL and HDL particles. This triglyceride can then be converted to free fatty acids by the actions of plasma lipases, primarily hepatic lipase. The net effect is a decrease in size and an increase in density of both LDL and HDL particles. Copyright 2001. The Endocrine Society. Reprinted with permission from Ref. 19.

of cholesteryl ester transfer protein, a significant amount of the triglyceride content of VLDL is exchanged for cholesterol in LDL particles, leading to the formation of triglyceride-enriched (and cholesterol-depleted) LDL (Figure 1).[19] These LDL particles are now primed to become smaller and denser through the actions of hepatic lipase-mediated triglyceride hydrolysis.[19,20] Thus, adverse changes in LDL particles occur as triglyceride levels increase. Once triglyceride levels exceed 100 mg/dl, small, dense LDL particles predominate (Figure 2).[23]

Is the Therapeutic Focus on LDL Cholesterol Justified?

LDL cholesterol is the primary target of lipid-lowering therapy in guidelines from both the ADA and the NCEP ATP III.[11,12] Once LDL cholesterol levels reach borderline-high levels (130–159 mg/dl), guidelines indicate that LDL-lowering therapy is a vital component of treatment to reduce cardiovascular risk, and it is particularly important if other risk factors are present.[11,12,24] As shown by the UKPDS investigators, a 39 mg/dl decrease in LDL cholesterol in subjects with diabetes was associated with a 36% reduction in CHD risk.[9] Current guidelines for patients with diabetes recommend statins as first-line lipid-lowering therapy.[11,12,24]

In patients with type 2 diabetes, statin therapy has been shown to significantly reduce LDL cholesterol, reduce elevated triglycerides, and modestly increase HDL cholesterol.[25–29] In large, randomized, controlled trials of statins in patients with type 2 diabetes, such as the Collaborative Atorvastatin Diabetes Study (CARDS) (n = 2,838), statin therapy was associated with significant reductions in LDL cholesterol of 40% and triglycerides of 19% and increases in HDL cholesterol of 1% relative to placebo (all, $P < 0.001$).[26]

In general, the therapeutic focus on LDL cholesterol lowering with statins is justified by clinical outcome results of randomized, controlled trials. Consistent, significant reductions in the incidence of major vascular events were observed in the diabetic population enrolled in CARDS (37%, $P = 0.001$) and in the diabetic subgroup (n = 5,963) of the Heart Protection Study (HPS) (22%, $P < 0.0001$).[25,26] In the HPS, diabetic patients with a pretreatment LDL cholesterol level of < 116 mg/dl (n = 2,426) had a significant 27% ($P = 0.0007$) reduction in risk of first major vascular events.[25] Overall, the Cholesterol Treatment Trialists' meta-analysis of > 90,000 patients in randomized statin trials found that in people with a history of diabetes (including those without a previous history of vascular disease), statins reduced the 5-year incidence of major coronary events by ~ 25% for each 39 mg/dl reduction in LDL cholesterol ($P < 0.0001$).[30]

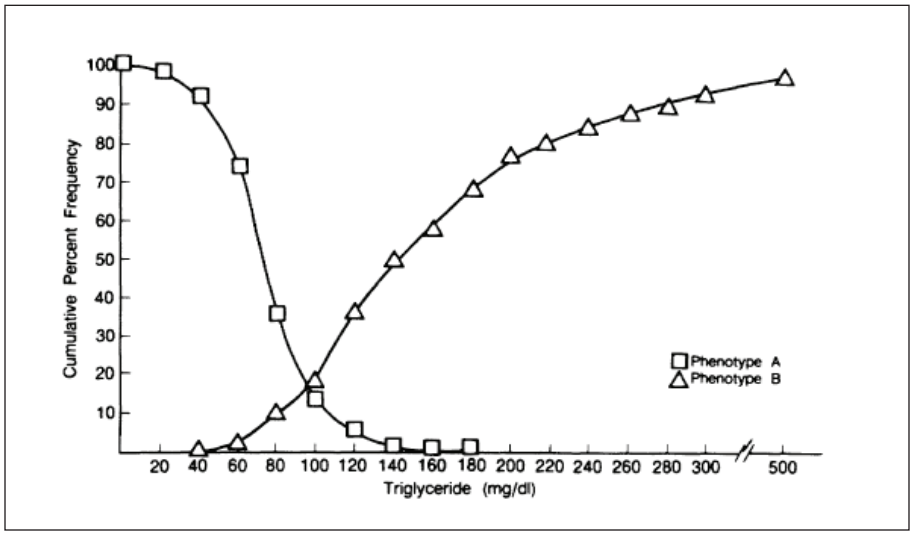

Figure 2. Cumulative distribution of adjusted triglyceride levels showing prevalence of LDL phenotype A (large, buoyant LDL particles) and phenotype B (small, dense LDL particles). Reprinted with permission from Ref. 23.

Is Intensive LDL Cholesterol Reduction With Statins Effective in Diabetes?

In treating people with diabetes, clinicians should carefully adhere to current treatment guidelines, which recommend reduction of LDL cholesterol to < 100 mg/dl regardless of baseline lipid levels.[12,17] Recent studies suggest that LDL lowering to < 70 mg/dl may provide even greater cardiovascular benefits, and the latest guidelines recommend < 70 mg/dl as an optional LDL goal in very–high-risk patients, such as those with diabetes and existing CVD.[11,31] Intensive lowering of LDL cholesterol may be necessary to achieve the 30–50% reductions in LDL cholesterol that guidelines recommend to bring most high-risk patients to goal.[31] When baseline LDL cholesterol is high (e.g., ≥ 160 mg/dl), a reduction of > 50% may be needed.[31]

Studies have confirmed that aggressive LDL reductions in patients with diabetes contribute to the achievement of LDL cholesterol goals. Significant reductions in other highly atherogenic lipids and lipoproteins, such as apolipoprotein B, non-HDL cholesterol, and triglyceride-rich lipoproteins, are also possible with intensive statin therapy.[28,29,32–34] Non-HDL cholesterol, which is composed of LDL cholesterol and VLDL cholesterol, is also a viable treatment target in patients with type 2 diabetes and "normal" LDL cholesterol levels. The NCEP ATP III guidelines consider non-HDL cholesterol a secondary treatment target (after LDL

cholesterol) in patients with elevated triglyceride levels (≥ 200 mg/dl), which includes many diabetic people, because it is a better measure of atherogenic cholesterol than LDL cholesterol alone.[12] The goal level for non-HDL cholesterol is 30 mg/dl higher than that for LDL cholesterol,[12] or < 130 mg/dl in diabetic patients.

In the Diabetes Atorvastatin Lipid Intervention study, intensive therapy with 80 mg atorvastatin was significantly ($P < 0.001$) more effective in lowering LDL cholesterol (–52%) and apolipoprotein B (–40%) than atorvastatin 10 mg (41 and 31%, respectively).[32] In the Use of Rosuvastatin Versus Atorvastatin in Type 2 Diabetes Mellitus study, 10–40 mg rosuvastatin significantly reduced lipid and lipoprotein fractions compared with 10–80 mg atorvastatin during 16 weeks, including LDL cholesterol (52 vs. 46%), non-HDL cholesterol (45 vs. 40%), and apolipoprotein (apo) B (45 vs. 40%) (all, $P < 0.0001$).[28] Both rosuvastatin (10–40 mg) and atorvastatin (20–80 mg) significantly reduced LDL cholesterol (54 and 48%, respectively), non-HDL cholesterol (50 and 44%, respectively), and the apoB/apoA1 ratio (41 and 36%, respectively) (all, $P < 0.001$ vs. placebo) in the 18-week Compare Rosuvastatin with Atorvastatin on ApoB/ApoA1 Ratio in Patients with Type 2 Diabetes Mellitus and Dyslipidemia study.[29] In studies of intensive statin therapy, the aggressive lipid treatment effects were also associated with significantly larger proportions (> 90%) of patients achieving LDL cholesterol goals.[28,29,33]

Data from the In the Simvastatin in Low HDL Cholesterol Diabetes Treatment Trial of Efficacy substudy ($n = 151$) showed that intensive statin therapy can also improve LDL particle composition in type 2 diabetes; 40 and 80 mg simvastatin lowered all four LDL subclasses by 19–48% ($P \leq 0.001$ vs. placebo) and can reduce the presence of atherogenic triglyceride-rich lipoproteins (lowering VLDL by 32–40% and intermediate-density lipoprotein by 53–57%; $P \leq 0.001$ vs. placebo).[34]

Is Intensive Statin Therapy Safe?

Despite the benefits of intensive statin therapy, clinicians may hesitate to fully implement this treatment strategy in patients with diabetes owing to safety concerns. Overall, standard doses of statins are well tolerated, and cases of muscle-related toxicity and elevated liver enzymes are low, particularly when standard doses are used in appropriately selected patients.[35–39] In large, randomized clinical trials with a large diabetic population, rates of these adverse events were no different than the rates observed with placebo.[26,40] Importantly, neither absolute LDL cholesterol level nor percentage decrease in LDL cholesterol appears to be linked to the risk of myopathy or rhabdomyolysis in statin-treated patients.[41] Data from the large Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 trial, for example, showed no relationship between achieved LDL cholesterol levels from 100 mg/dl to as low as < 40 mg/dl and the frequency of adverse events.[42] Moreover, patients with LDL cholesterol levels ≤ 60 mg/dl (17–25% of whom had diabetes) had significantly fewer major cardiac events than did patients whose achieved LDL levels were between 80 and 100 mg/dl (Figure 3).[42]

In general, experts believe that muscle injury from statin therapy is related to the plasma concentration of the statin (which is influenced by the drug's pharmacokinetics and potential for drug-drug interactions), statin dose, and the patient's risk factors.[41] When administered at recommended doses, the more efficacious statins (atorvastatin, rosuvastatin) have a risk of rhabdomyolysis similar to that observed with less potent agents.[30,35,39]

Conclusions

Diabetes carries an exceptionally high burden of disease, including a higher mortality from CVD. Primary cardiovascular prevention is particularly important in this population because diabetic individuals suffering a first MI are much more likely to die than are their nondiabetic counterparts. Adherence to lipid guidelines is crucial to improving clinical outcomes in diabetic patients. A number of roadblocks to the successful implementation of lipid guidelines have

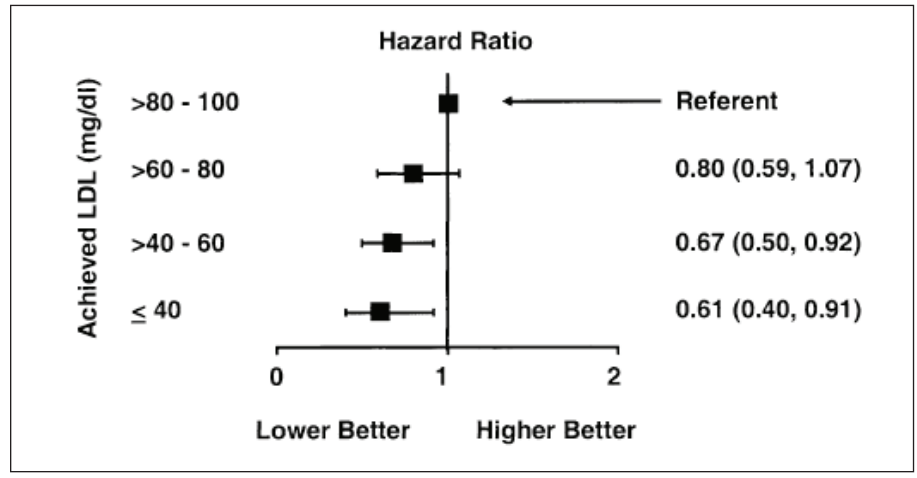

Figure 3. Hazard ratios for the primary end point by subgroup of achieved LDL cholesterol (adjusted for age, sex, baseline calculated LDL cholesterol, diabetes, and prior MI) in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 trial. Reprinted from Ref. 42 with permission from Elsevier.

been identified. Among the most common are failure to recognize that *1*) the borderline LDL cholesterol elevations common in diabetic patients are associated with substantial cardiovascular risk because of their small, dense composition and the high CHD risk already present in this population; *2*) seemingly mild abnormalities in LDL cholesterol interact with other lipid abnormalities to further heighten risk; and *3*) intensive LDL cholesterol reduction in this setting results in significant reductions in cardiovascular morbidity and mortality. Indeed, the opportunity to substantially improve cardiovascular outcomes by assessing and treating the atherogenic diabetic dyslipidemia characteristic of this population should not be missed.

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