Management of Cholesterol in Diabetes—A Review

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Abstract
Diabetes is considered to be equivalent to coronary artery disease in terms of cardiovascular risk. Therefore, aggressive management of cardiovascular risk factors, especially dyslipidemia, is warranted in patients with diabetes. Although diabetes is associated with a specific lipid pattern (increased triglycerides, reduced high-density lipoprotein [HDL] cholesterol, and presence of small dense low-density lipoprotein [LDL] particles), LDL cholesterol lowering remains the primary target of lipid management. Lifestyle intervention should be the first-line therapy in dyslipidemia management, and a statin should be considered early on, aiming not only at reaching target LDL cholesterol levels (<70mg/dl in patients with and <100mg/dl in patients without concomitant cardiovascular disease), but more importantly at slowing the progression of atherosclerosis and reducing the rate of cardiovascular events. Combination therapy for optimal LDL reduction and achievement of other lipid goals (triglyceride reduction and HDL increase) can be considered in patients with diabetes who are at extremely high cardiovascular risk.

Keywords
Diabetes, cholesterol, diabetic dyslipidemia, low-density lipoprotein cholesterol, coronary artery disease

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Diabetes and Cardiovascular Disease
Diabetes has long been recognized as a major risk factor for cardiovascular disease and is widely regarded as a ‘coronary disease equivalent,’ as diabetes and established coronary heart disease indicate a similar absolute risk for cardiovascular death in both men and women. Cardiovascular complications of diabetes have traditionally been regarded as either microvascular (retinopathy, nephropathy, and neuropathy) or macrovascular (coronary, cerebrovascular, peripheral, and renal atherosclerosis); the latter have been held responsible for up to 70% of diabetes-associated mortality. Not only is cardiovascular disease more common in patients with diabetes, it also occurs at a younger age, presents with more atypical symptoms, and has a less favorable course: diabetic survivors of a myocardial infarction have a higher short- and long-term mortality rate and are more likely to develop heart failure than non-diabetics. The pathophysiology of diabetes-promoted atherosclerotic disease is complex and multifactorial. It comprises a direct influence of diabetes on vascular structure and function as well as a complex interplay of traditional and novel (especially inflammatory and hemostatic) cardiovascular risk factors with diabetes-associated metabolic derangements as a likely source of interaction—the cardiometabolic syndrome. Among these risk factors, diabetic dyslipidemia is probably the most exhaustively studied and has been traditionally recognized as both a significant co-factor in the development of and a pivotal therapeutic target in the fight against cardiovascular diseases in diabetes.

Diabetic Dyslipidemia
Also referred to as atherogenic dyslipidemia, diabetic dyslipidemia is characterized by a triad of lipid derangements: moderate elevation of triglyceride levels, decreased high-density lipoprotein (HDL) cholesterol levels, and presence of small dense (oxidation-prone and thus extremely atherogenic) low-density lipoprotein (LDL) particles. According to data from the Framingham cohort, 19% of men and 17% of women with diabetes (as opposed to only 9 and 8% of men and women without diabetes, respectively) have triglyceride levels above the 90th percentile of the general population, and similarly twice as many participants with diabetes than those without (21 versus 12% in men and 25 versus 10% in women) have HDL levels below the 10th percentile; conversely, high total and LDL cholesterol levels affect those with and those without diabetes to the same extent. Diabetic dyslipidemia confers an estimated risk comparable to that of an LDL concentration between 150 and 220mg/dl. This lipid pattern (and especially the presence of small dense LDL) is more characteristic of type 2 than type 1 diabetes: in the latter, the introduction of insulin therapy and glycemic control can restore the lipid profile; in the former, lipid abnormalities not only pre-date the onset of full-blown type 2 diabetes (suggesting that insulin resistance rather than lack of insulin action is the principal etiologic mechanism), but also persist despite tight glycemic control. Several factors have been deemed responsible for diabetic dyslipidemia: insulin effects on liver apoprotein production,
regulation of lipoprotein lipase, actions of cholesteryl ester transfer protein, and peripheral effects of insulin on adipose and muscle tissue.20

However, despite being more prevalent in patients with diabetes, hypertriglyceridermia failed to independently predict coronary events in the UK Prospective Diabetes Study.21 The strongest predictor of coronary artery disease was LDL cholesterol followed by HDL cholesterol. This supports current guideline recommendations that LDL cholesterol should be the primary lipid target in patients with diabetes. Despite being equally prevalent in individuals with and without diabetes,21 increased LDL cholesterol in diabetes deserves particular attention because of its additive interplay with diabetes, increasing cardiovascular risk in this population.

Goals of Therapy

Cardiovascular risk is a continuous variable. For cholesterol levels, especially LDL, the relationship between plasma concentration and the rate of cardiovascular events is virtually linear22 with every lowering of LDL by 40mg/dl (1mmol/l), a proportionate 20% reduction in major cardiovascular events over five years is expected.23 Thus—at least in terms of cholesterol reduction—a ‘the lower, the better’ approach should be considered. However, in clinical practice different categories of risk have been established in order to help clinicians select patients whom a preventive measure would benefit the most (and harm the least).

The primary goal is reduction of LDL cholesterol to below 100mg/dl (below 70mg/dl if feasible, and especially if the patient has both diabetes and cardiovascular disease). Current guidelines acknowledge the high cardiovascular risk associated with diabetes in both primary (>20% 10-year risk for cardiovascular events) and secondary prevention settings (worse prognosis of coronary disease in patients with diabetes), and therefore recommend that diabetes be regarded as a coronary artery disease equivalent.1 The rule of thumb for introduction of pharmacologic therapy in patients with diabetes but no cardiovascular disease is therefore the same cut-off as for those with coronary artery disease: 100mg/dl. However, this is an oversimplification as significant differences in terms of cardiovascular risk exist within diabetic populations, and clinical judgment should always be applied. At one extreme are young patients with well controlled diabetes in whom the effectiveness of statin therapy has not been established by evidence-based medicine standards, and at the other extreme are patients with diabetes and concomitant cardiovascular disease in whom cardiovascular risk is extremely high and the benefits of lipid-lowering therapy are especially pronounced; for this group of patients the target level for LDL has been set even lower, at <70mg/dl.21 This is based on findings from the Heart Protection Study (HPS)24 and the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22)25 trials. In the former, simvastatin therapy significantly reduced the risk in patients with baseline LDL levels below 100mg/dl (especially in extreme-risk patients, such as those with diabetes and concomitant cardiovascular disease), while in the latter high-dose atorvastatin, by lowering LDL levels to a median of 62mg/dl, achieved significantly greater risk reduction than pravastatin, which lowered LDL ‘only’ to a median of 95mg/dl. Accordingly, the cut-off level for introduction of pharmacologic therapy has been lowered from >130 to >100mg/dl.

The secondary goal is reduction of non-HDL cholesterol—LDL cholesterol, lipoprotein (a), intermediate and very low density lipoproteins—to below 130mg/dl. Only if triglyceride levels exceed 500mg/dl does management of the hypertriglyceridermia supersede other lipid goals because of the increased risk for pancreatitis.

The tertiary goal is increasing HDL cholesterol, which needs to be addressed in high-risk individuals with non-HDL cholesterol within the recommended concentration range and with HDL levels below 40mg/dl. However, no specific target levels for HDL were established in the guidelines.

The American Diabetes Association (ADA) has set the desirable LDL, HDL, and triglyceride levels at <100mg/dl, >40mg/dl (>50mg/dl in women), and <150mg/dl, respectively. Similar to the guidelines of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the ADA guidelines recommend that LDL reduction be the primary goal of dyslipidemia management in diabetes, and originally proposed pharmacologic intervention in individuals with LDL cholesterol above 130mg/dl. In 2005, a revised statement26 including new evidence again supporting a ‘the lower, the better’ approach suggested that a reduction of LDL may be appropriate irrespective of baseline cholesterol levels, thus de facto harmonizing recommendations with NCEP ATP III.

Management of Dyslipidemia in Diabetes

The aim of dyslipidemia management is reduction of cardiovascular mortality. Lipid lowering is widely regarded as a surrogate indicator of cardiovascular risk reduction; dyslipidemia management is therefore primarily aimed at lowering LDL cholesterol either by lifestyle measures or by a combination of lifestyle measures and pharmacologic therapy.

Lifestyle Modification

Lifestyle intervention includes diet, exercise, and weight management. Both diet and exercise can ameliorate diabetes-associated lipid derangements, namely decreasing triglyceride and increasing HDL cholesterol levels, and can even accomplish a moderate reduction of LDL.27 Dietary recommendations for lowering LDL cholesterol include reduced intake of saturated and trans-saturated fats (<7% of daily calories) and cholesterol (<200 mg/day) and increased intake of fiber (10–25g daily) and plant sterols (2g daily).1,15 In patients with increased triglyceride levels and low HDL cholesterol, a reduction of carbohydrate intake (<60% of daily calories) is also recommended.1 Additionally, patients with diabetes are recommended to take at least 150 minutes of moderate aerobic exercise per week.28 A major limitation of non-pharmacologic measures is their moderate effectiveness: diet alone can achieve only a 5–15% reduction of LDL,26,27 which usually does not allow the patient to reach target values. Moreover, non-pharmacologic measures are characterized by modest implementation and poor long-term adherence.29 Nonetheless, lifestyle intervention, despite being only moderately effective at a population level, may make a significant contribution to risk management in individual patients. Diet also improves the effectiveness of pharmacologic therapy.30 Lastly, all trials of pharmacologic therapy also added appropriate lifestyle measures, thus rendering lifestyle intervention a compulsory element of all lipid-lowering approaches.
Pharmacologic Management—Evidence from Clinical Trials
Hydroxy-methyl glutaryl coenzyme A reductase inhibitors (statins) are first-line agents in the management of dyslipidemia in patients with diabetes given not only their efficacy in lowering LDL cholesterol but especially their efficacy in reducing cardiovascular morbidity and mortality, which is now supported by an overwhelming body of evidence. Fewer studies have assessed the efficacy of fibrates or niacin in this regard, and the outcome data for fibrates are quite mixed.

Statins
Several large randomized, double-blind, placebo-controlled clinical trials for both primary and secondary prevention have demonstrated the efficacy of statins in reducing cardiovascular morbidity and mortality, with similar relative (but obviously greater absolute) benefits in patients with and without diabetes.

Early statin trials—namely the Scandinavian Simvastatin Survival Study (4S), the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, the Cholesterol And Recurrent Events (CARE) trial, and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial—suggested a significant reduction in coronary events in patients with diabetes treated with either simvastatin or pravastatin, but most of them were underpowered (and thus prone to post hoc analysis bias) to draw conclusions for diabetic populations.

The Heart Protection Study (HPS) was the first statin trial to prospectively include enough patients with diabetes to infer adequate pre-specified subgroup analysis, and was soon followed by the Collaborative Atorvastatin Diabetes Study (CARDS), the first statin trial conducted only in patients with diabetes. In HPS, 5,963 patients over 40 years of age with diabetes (2,912 of whom had no known cardiovascular disease) were randomized to 40mg of simvastatin or placebo; treatment with simvastatin 40mg was associated with a 22% relative risk reduction for cardiovascular events (20.2% in the simvastatin-allocated versus 25.1% in the placebo-allocated group; 

The biologic rationale for using fibrates in patients with diabetes is very strong: as fibrates improve diabetic dyslipidemia (by reducing triglyceride levels by 20–50% and increasing HDL cholesterol by 10–20% with only moderate effects on LDL cholesterol) and also halt angiographic progression of atherosclerosis, their effect should translate into a reduction of clinical events. Although early studies (including subgroups of patients with diabetes) suggested a reduction of cardiovascular risk with fibrate therapy, two recent trials failed to demonstrate a substantial impact of fibrates on cardiovascular events in patients with type 2 diabetes.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial randomized 9,785 statin-naïve patients with type 2 diabetes (2,131 of whom had known cardiovascular disease) to either 200mg micronized fenofibrate daily or placebo. After five years of follow-up, no significant difference in the primary end-point (coronary events) could be detected, while the 11% relative risk reduction for cardiovascular events (p=0.035) was mainly driven by a reduction in non-fatal infarctions and revascularizations. Failure of fenofibrate to reduce cardiovascular risk more substantially was principally attributed to a higher proportion of patients starting a statin in the placebo group.

The lack of substantial effects of fibrates on cardiovascular outcomes was corroborated by the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial. ACCORD Lipid randomized 5,518 patients with type 2 diabetes on simvastatin to receive either fenofibrate or placebo. Over a mean follow-up of 4.7 years, no significant differences in either the primary composite outcome (major cardiovascular events, which occurred in 2.2% of patients in the fenofibrate and 2.4% of...
patients in the placebo group; \(p=0.35\) or in any of the secondary outcomes\(^1\) could be detected between the fenofibrate and the placebo group. However, a subgroup analysis suggested a possible benefit for patients with both high baseline triglyceride levels and low baseline HDL cholesterol levels.

**Niacin**

Niacin is another drug with promising effects on diabetic dyslipidemia: it increases HDL by 15–35% and reduces triglycerides by 20–50%.\(^1\) Niacin fell out of favor among lipidologists because of its side effects (namely the niacin rash), despite being one of the first lipid-lowering drugs to show a substantial reduction in cardiovascular events.\(^1\) With extended-release formulations and the addition of laropiprant, a reduction in occurrence and intensity of niacin rash will probably favor more widespread use of niacin in clinical practice.\(^2\) However, in the two decades of its absence from the lipid-lowering scene, statins have accumulated so much evidence in terms of cardiovascular prevention that niacin will probably remain an adjunct therapy.

**Ezetimibe**

Ezetimibe inhibits enteral absorption of cholesterol, therefore exercising lipid-lowering action complementary to statin therapy (dual inhibition). Thus, addition of ezetimibe to a statin has been shown to lower LDL more efficiently and help to achieve LDL goals more often than statin monotherapy.\(^4\) However, no trial to date has shown that addition of ezetimibe might provide additional cardiovascular protection by reducing the rate of clinical events.

**Combination Therapy**

The rationale behind addition of a second or third agent to lipid-lowering monotherapy (by default a statin) is that further lipid lowering will only yield optimal LDL cholesterol, but will also more likely achieve all three lipid goals. However, clinical trials have yet to prove that a persuasive efficacy of various combination therapies outweighs the risks and complexity of such an approach.

In line with the primary goal of dyslipidemia management in preventive cardiology, a statin should always be the first-line therapy. In patients at highest cardiovascular risk, a combination therapy aimed either at optimization of LDL levels (statin plus ezetimibe) or, in patients who already have optimal levels of LDL, at achievement of other lipid goals (statin plus niacin) seems plausible, provided the patient can be closely monitored for adherence and possible side effects.

**Conclusions**

Diabetes is a metabolic disorder associated with a specific type of atherogenic dyslipidemia. LDL lowering remains the cornerstone of preventive cardiology, and statin therapy the most useful tool to achieve it. Nonetheless, re-introduction of ancillary drugs (such as niacin) promises a revival of diabetic dyslipidemia management, which has been partially neglected because of the lack of effective therapies to counteract it.

Another challenge is lipid management in younger patients with diabetes. Patients with type 1 diabetes have traditionally been excluded from major trials of cardioprotective drugs; even the largest data set of statin efficacy in diabetic populations (the HPS trial) excluded patients below 40 years of age. This is especially worrisome in light of the global pandemic of type 2 diabetes in younger adults.

Proactively the most challenging issue, however, remains an individualized approach to cardiovascular risk management. Categories of risk are becoming more and more complex, and managing patients solely based on presence or absence of diabetes (or LDL above or below a certain cut-off) is becoming obsolete. Individualized preventive cardiology will demand a more complex yet more effective approach to cardiovascular risk reduction in patients with diabetes, including non-LDL lipid management and combination therapies.

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