Management of Dyslipidemia in Patients with Diabetes

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Abstract

Cardiovascular disease is the leading cause of major morbidity and mortality in patients with type 2 diabetes. The recent focus on the apparent lack of cardiovascular benefit associated with glucose-lowering strategies has overshadowed the importance of targeting dyslipidemia for cardiovascular prevention in patients with diabetes. While lowering low-density lipoprotein (LDL) cholesterol is beneficial, diabetes is also characterized by hypertriglyceridemia, low levels of high-density lipoproteHDL-cholesterol and abundant levels of small, dense LDL particles. Accordingly, these factors represent additional targets for therapeutic modification in order to achieve more effective reductions in cardiovascular risk.

Keywords

Diabetes mellitus, insulin resistance, diabetic dyslipidemia, hypertriglyceridemia, low HDL-cholesterol, LDL-cholesterol-lowering therapy, statin

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In association with the global spread of abdominal adiposity, the worldwide prevalence of type 2 diabetes continues to increase.[1] This is one of the pivotal factors underscoring the projection that cardiovascular disease will become the leading cause of mortality worldwide by 2020. Diabetes is associated with an adverse clinical outcome in individuals with and without established cardiovascular disease.[2–4] These observations have promoted the concept that diabetes should be considered a coronary risk equivalent in guidelines for cardiovascular prevention. They also identify individuals who are more likely to derive greater benefit from the use of more intensive preventive therapies.

Considerable attention has focused on determining whether improvement of glycemic control is associated with cardiovascular benefit in patients with diabetes. The findings from recent clinical trials have, however, failed to demonstrate any reduction in macrovascular events.[5–7] Despite this, clinical trials have consistently reported cardiovascular protection in association with lowering levels of low-density lipoprotein cholesterol (LDL-C).[8–12] While LDL-C lowering has become increasingly integrated into clinical strategies for the prevention of cardiovascular disease, there remains a substantial residual risk of clinical events.

It has been proposed that the presence of additional dyslipidemic features contributes to ongoing vascular risk in patients with diabetes.[13–16] These features include hypertriglyceridemia, low levels of high-density lipoprotein cholesterol (HDL-C) and abundant circulating levels of small, dense LDL particles. Accordingly, each of these abnormal lipid states has emerged as an attractive target for therapeutic manipulation.

The Characteristics of Dyslipidemia in Patients with Diabetes

Despite the finding that lowering LDL-C is beneficial in patients with diabetes, LDL-C levels are typically not found to be elevated. In contrast, a number of additional lipid parameters have been found to be abnormal in patients with diabetes, including hypertriglyceridemia, low levels of HDL-C and a greater number of circulating small, dense, LDL particles.[13–16] Small, dense forms of LDL may be particularly atherogenic due to a greater avidity to diffusion into the artery wall and subsequent oxidation. This may reflect a level of circulating LDL that is associated with considerable vascular risk, despite having an apparently well-controlled LDL-C level. Furthermore, it may also contribute to the unequivocal benefit of LDL-C-lowering strategies in patients with type 2 diabetes.

While the precise mechanisms that underscore the presence of this dyslipidemic profile in diabetes remain to be completely elucidated, insulin resistance appears to have an adverse impact on the secretion of apolipoprotein (apo) B-containing particles and lipoprotein remodeling.[17,18] In combination, these lipid abnormalities are likely to confer an adverse effect on the artery wall and increase overall cardiovascular risk.

Management of Diabetic Dyslipidemia

Lifestyle interventions—including diet, physical activity, weight loss and smoking cessation—remain the cornerstone of all approaches to management of patients with diabetes. Although lifestyle intervention can improve diabetic dyslipidemia to some extent,[19,20] it remains difficult to achieve optimal goals. The addition of pharmacologic therapy will be needed in many patients. Dyslipidemia is also partially corrected by

control of hyperglycemia, but abnormalities persist, partly due to the effects of insulin resistance on lipoprotein metabolism. Current management strategies in diabetes patients with atherogenic dyslipidemia focus on lowering the LDL-C level by at least 30–40 %, with a statin as the preferred drug, together with lifestyle intervention to reduce cardiovascular risk.[21]

Pharmacologic Strategies for Lipid Modification

Statins

Pharmacologic inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) are the most important advance in the treatment of lipid disorders. Statins are considered first-line therapy for the treatment of dyslipidemia because they have significant clinical benefit in patients with and without diabetes. A *post hoc* analysis of the Heart Protection Study examined the effects of simvastatin 40 mg or placebo on cardiovascular events in people with diabetes.[10] Simvastatin reduced the incidence of coronary events by 27 % ($p<0.0001$) and the incidence of any major vascular events by 24 % ($p<0.0001$).

The Collaborative Atorvastatin Diabetes Study was the first prospective placebo-controlled trial of statin therapy in patients with type 2 diabetes and no history of cardiovascular disease.[8] The incidence of major cardiovascular events was reduced by 37 % with atorvastatin 10 mg ($p=0.001$). In addition to this, fatal and nonfatal strokes were reduced by 48 % and total mortality was reduced by 27 % ($p=0.059$).

A meta-analysis of 14 randomized trials of statin therapy in patients with diabetes showed a 9 % reduction in all-cause mortality per mmol/L reduction in LDL-C ($p=0.02$).[22] There was also a 21 % reduction in major vascular events per mmol/L reduction in LDL-C. The results in individuals with diabetes were comparable to those without the disease.

The Treating to New Targets study assessed the efficacy and safety of lowering LDL-C <80 mg/dL with a high-dose statin in patients with stable coronary artery disease.[23] A *post hoc* analysis was carried out of the patients with diabetes in this study. The analysis showed the favorable efficacies of high-dose statin (atorvastatin 80 mg) for several primary endpoint components—non-procedure-related myocardial infarction (MI), fatal/nonfatal stroke and cardiac-death—compared with low-dose statin (atorvastatin 10 mg).[9] The atorvastatin 80 mg group had a 22 % relative reduction in the primary endpoint compared with the atorvastatin 10mg group ($p<0.001$). Significant differences favoring atorvastatin 80 mg were also found for cerebrovascular events ($p=0.037$) and any cardiovascular event ($p=0.044$). These results support the use of high-dose statins as an appropriate therapeutic option in patients with diabetes and cardiovascular disease.

Overall, these statin trials confirm that LDL-C reduction in patients with diabetes will reduce major cardiovascular events, including stroke, whether or not the patients have established coronary artery disease. Thus, LDL-C is still a main target for the reduction of cardiovascular events in patients with diabetes.

Lipid Modification Beyond Statins

Despite optimal statin therapy, a residual cardiovascular risk persists in patients with diabetes, who continue to demonstrate substantial event rates in clinical trials. The results from intravascular ultrasound trials show accelerated plaque progression within the coronary artery despite the use of medical therapies including a statin.[24]

While there is an ongoing search to develop additional LDL-C-lowering therapies, interventions that also target dyslipidemic states, such as low levels of HDL-C and hypertriglyceridemia, may reduce the burden of cardiovascular disease.

Fibrates

Fibrates are agonists of peroxisome proliferator-activated receptors (PPAR-α), which regulate the expression of specific target genes that control lipid metabolism and inflammatory cascades.[25] Although fibrates have a minimal impact on LDL-C levels, they:[26–28]

- decrease triglycerides and very(V)LDL levels;
- increase HDL production; and
- promote a shift from small, dense atherogenic LDL particles to larger and potentially less atherogenic LDL particles.

Early studies that investigated the impact of fibrates on disease progression and cardiovascular events were encouraging. In the Diabetes Atherosclerosis Intervention Study, fenofibrate therapy was associated with less angiographic progression of atherosclerotic lesions in patients with diabetes, suggesting a benefit at the vessel wall level.[29] In studies of both primary and secondary prevention, *post hoc* analysis revealed that treatment with gemfibrozil was associated with reductions in coronary events of 71 % and 34 %, respectively, in patients with type 2 diabetes.[30,31] Additional analyses revealed that modest elevations in HDL-C, but not triglyceride lowering, were independent predictors of the clinical benefit of gemfibrozil in these studies.

With increasing use of statins, it became apparent that gemfibrozil was not well tolerated in combination, highlighting the need to find an alternative fibrate for clinical use. Despite the initial benefit on angiographic disease progression observed with fenofibrate, subsequent studies of its effect on cardiovascular events have been disappointing.

The Fenofibrate Intervention and Event Lowering in Diabetics study assessed the effects of fenofibrate compared with placebo on cardiovascular events in patients with type 2 diabetes.[32] In this study, fenofibrate failed to significantly reduce the risk of the primary outcome of coronary events. This was despite a *post hoc* analysis suggesting a benefit for diabetes patients with both elevated triglyceride levels and low HDL-C levels. The rationale for the lack of efficacy of fenofibrate in this study has not been fully elucidated. Background statin use was not mandated, resulting in an imbalanced drop in use during the course of the study. The differences in statin use were not, however, able to reconcile the lack of efficacy observed in the study.

Given that statins and fibrates have complimentary effects on dyslipidemia, their combination would seem to be particularly useful in the management of atherogenic dyslipidemia associated with type 2 diabetes. The combination of statins and fibrates has shown superior lipid-modifying efficacy compared with statin monotherapy in reducing triglycerides, VLDL-C and non-HDL-C levels, as well as raising HDL-C levels.[33,34]

These findings, in addition to the widespread use of statins for risk reduction in all patients with type 2 diabetes given their status as coronary risk equivalents, mandated the need to evaluate the impact of fibrate therapy in addition to background statin treatment in a large clinical trial. The Action to Control Cardiovascular Risk in Diabetes trial compared the efficacy of simvastatin plus fenofibrate with simvastatin alone on cardiovascular morbidity and mortality.[35] Fenofibrate, when administered in addition to statin therapy, did not reduce the rate of cardiovascular events when compared with simvastatin alone. Of interest, clinical benefit was observed in patients with hypertriglyceridemia and low HDL-C levels (triglyceride level >204 mg/dl and HDL-C level <34 mg/dl) at baseline. This finding has been consistently demonstrated in all trials of fibrate therapy. This was further illustrated in a recent meta-analysis that revealed a statistically significant reduction in cardiovascular events of 10 % with fibrate therapy.[36] Accordingly, fibrates continue to represent a reasonable therapeutic option for diabetic patients with either hypertriglyceridemia or low HDL-C levels.

Niacin

Among currently used lipid-modifying agents, niacin is the most potent agent available to increase HDL-C levels. Studies show that niacin treatment has some beneficial efficacies on the incidence of MI or progression of coronary artery stenosis and carotid intima-media thickness.[37–41] A recent study compared the efficacy of a statin plus extended-release niacin with a statin plus ezetimibe in patients with coronary artery disease.[42] The results showed a significant regression of carotid intima-media thickness and major cardiovascular events in the niacin plus statin group compared with the statin plus ezetimibe group. This effect was consistent, even in patients with diabetes.

While concerns have always been expressed with regard to a worsening of glucose control in diabetes patients, niacin can be used in most patients without any overt changes in metabolic homeostasis.[43,44] The potential benefit of more widespread use of niacin in patients with type 2 diabetes will be apparent when the results of two large clinical trials of its effect on cardiovascular outcomes are reported in the next few years.

Ezetimibe

Ezetimibe lowers LDL-C by inhibiting the intestinal absorption of cholesterol without affecting the absorption of triglycerides or fat-soluble vitamins.[45] It is able to reduce LDL-C by 15–25 % when given as monotherapy or added to ongoing statin treatment.[46] The complementary mechanisms of action of ezetimibe and statins and their additive effects on LDL-C lowering mean that their combination is widely used.

The second analysis of the Stop Atherosclerosis in Native Diabetics Study has been caried out. It examines the effects of lowering LDL-C using statins alone versus statins plus ezetimibe on common carotid artery intima-media thickness in patients with type 2 diabetes and no prior cardiovascular event.[47] This study showed that equivalent LDL-C reductions with a statin plus ezetimbie or a statin alone resulted in similar regression of common carotid artery intima-media thickness.

The combination of ezetimibe plus simvastatin was recently demonstrated to reduce cardiovascular morbidity in patients with chronic kidney disease.[48] Its effects in a broader population following an acute coronary syndrome, many of whom will have type 2 diabetes, continues to be investigated in an ongoing clinical trial.[49]

Thiazolidinediones

The thiazolidindiones are PPAR-γ agonists that were developed for their insulin-sensitizing properties. They are able to effectively lower glucose concentrations in patients with type 2 diabetes.[50,51] Although these agents are not indicated for the treatment of dyslipidemia, considerable data suggest that their lipoprotein effects may contribute to their impact on cardiovascular outcomes.[52–55] Such effects include lowering triglycerides, raising HDL-C and promoting the shift from small to large LDL particles, in addition to their anti-inflammatory effects. Cardiovascular trials of the two major agents used in clinical practice have, however, demonstrated markedly different effects on outcomes.

The Prospective pioglitazone clinical trial in macrovascular events (PROactive) study examined the effect of pioglitazone on cardiovascular events in patients with type 2 diabetes.[56] Pioglitazone-treated patients demonstrated a non-significant reduction in the composite endpoint of death, nonfatal MI, stroke, acute coronary syndrome, coronary or peripheral revascularization, or limb amputation (p=0.095).

Considerable debate has focused on the potential contribution of peripheral arterial endpoints to the overall result of the study. This has been further highlighted by the finding that pioglitazone was associated with a significant reduction in the combination of death, nonfatal MI and stroke (11.5 % versus 13.6 % with placebo, p=0.045). These results have been backed up by the observation that the primary composite endpoint was reduced by pioglitazone in higher risk patients with a history of previous MI.

The potential benefit on major ischemic events in the coronary and cerebrovascular territories was further highlighted by the demonstration that pioglitazone treatment has a beneficial impact on disease progression in the artery wall. Previous studies have demonstrated that patients with type 2 diabetes harbor an accelerated form of plaque progression, even in the setting of statin therapy.[24]

More recently, the impact of pioglitazone on ischemic events was studied in the Carotid Intima-medial Thickness in Atherosclerosis using Pioglitazone and Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation trials. These demonstrated that pioglitazone slows the progression of carotid intima-medial thickness and coronary atherosclerosis, respectively, when compared with glimepiride.[57,58]

Subsequent analyses have revealed that the beneficial impact of pioglitazone on HDL-C and triglyceride levels is due to the agent's contribution at the level of the artery wall.[59] This further emphasizes the importance of atherogenic dyslipidemia as a target for modification in patients with type 2 diabetes.

The effects of rosiglitazone on cardiovascular outcomes have been less positive than pioglitazone. While initially brought to market on the basis of its glucose-lowering properties, small signals in several clinical trials

suggested it had a potentially harmful effect on the risk of myocardial infarction. This was confirmed in a highly publicized meta-analysis by Nissen and Wolski.[60,61] While other groups, using different statistical approaches to their analysis suggested a lack of statistical significance for this relationship, the overall trend towards potential harm was consistent across all studies.

While an outcome study was conducted to evaluate rosiglitazone, interim analysis following premature cessation failed to demonstrate any adverse effect, although the authors had concluded that there was no real power to demonstrate a deleterious effect.[62] The results of this study may have been attributed to the adverse effect of rosiglitazone on LDL-C, phospholipase A2[63] and the expression of atherosclerosis-related genes, including matrix metalloproteinases.[64] On the basis of ongoing uncertainty regarding any evidence of clinical benefit, the use of rosiglitazone has been severely restricted.

There continues to be enthusiasm to develop new PPAR agonists that act as more powerful pharmacological agonists or activate multiple pathways.[65] A combined PPAR-α/γ agonist might have a beneficial impact on lipids, glycemic control and inflammatory cascades. While early dual PPAR agents have been removed due to adverse clinical outcomes, a new agent called aleglitazar is being evaluated in diabetes patients following acute coronary syndromes.

Omega-3 Fatty Acids

Omega-3 fatty acids lower triglyceride levels. In addition to this, they have various effects on arrhythmia, platelet aggregation, inflammation, endothelial function and blood pressure. In some studies, the combination of omega-3 fatty acids and a statin have significantly reduced triglycerides, VLDL and non-HDL-C levels compared with a statin alone.[66–68] Despite this, the data regarding the clinical efficacy of omega-3 fatty acids in terms of morbidity and mortality are still controversial.

Three large trials—Gruppo Italiano per lo Studio della Sopravvivenza nell'Infartio miocardico-Prevenzione (GISSI-Prevenzione), Japan EPA Lipid Intervention Study and GISSI-heart failure—have shown the positive clinical outcomes of omega-3 fatty acids.[69–71] A recent systematic review did not, however, demonstrate a clear effect on total mortality or combined cardiovascular events.[72]

The Outcome Reduction with an Initial Glargine Intervention study is looking to determine whether omega-3 fatty acids reduce cardiovascular death compared with placebo in more than 12,000 patients with dysglycemia.[73]

Cholesteryl Ester Transfer Protein Inhibition

Cholesteryl ester transfer protein (CETP) plays an important role in cholesterol metabolism via the transfer of esterified cholesterol from HDL to VLDL and LDL.[74] Studies of Japanese populations with CETP deficiency identified high HDL-C levels, which led to the development of drugs targeting CETP activity as a means to substantially elevate HDL-C levels and potentially decrease cardiovascular risk.[75,76]

The findings from early clinical trials of the CETP inhibitor torcetrapib were not good. Patients had elevations in blood pressure and an increased risk of cardiovascular morbidity and mortality despite considerable increases in HDL-C and lowering of LDL-C.[77,78] There was no slowing of the progression of carotid intima-medial thickness and coronary atherosclerosis.

Subsequent findings of off-target toxicities of torcetrapib, functional HDL and regression at the highest levels of HDL-C has led to the ongoing investigation into the impact of additional CETP inhibitors that appear to lack such toxicity.[79] These agents are currently being evaluated in large clinical trials.

Phospholipase A2 Inhibitors

Members of the phospholipase family are involved in the hydrolysis of phospholipids at the sn-2 position and play a critical role in the generation of prostaglandin intermediates.[80,81] Accordingly, these factors have been implicated in the orchestration of a range of inflammatory pathways.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is an important regulator of lipid metabolism and inflammation. It circulates with lipoprotein particles and is carried into the arterial wall with LDL particles during the progression of atherosclerosis.[82,83] Epidemiologic studies demonstrate that elevated circulating levels of Lp-PLA2 are associated with an increased risk of MI and stroke.[84,85] Histologic examination of diseased human coronary arteries reveals an intense presence of the enzyme in atherosclerotic plaques that are prone to rupture.[86]

Early-phase clinical studies showed that the pharmacological Lp-PLA2 inhibitor darapladib decreased plasma Lp-PLA2 activity and interleukin-6 levels compared with placebo.[87] They also showed that the inhibitor had a favorable effect on the size of the necrotic core in both porcine and human atherosclerosis.[88] The clinical effect of darapladib is being evaluated in large outcome studies.

Secretory phospholipase A2 (sPLA2) is implicated in the generation of bioactive lipid intermediates. Evidence from both atherosclerosis staining and population studies associates sPLA2 with cardiovascular risk.[89–92] Administration of the sPLA2 inhibitor varespladib in early studies demonstrated favorable effects in animal models of atherosclerosis. There were reductions in levels of LDL-C and C-reactive protein in addition to sPLA2 activity in statin-treated patients with atherosclerosis.[93] The impact of varespladib on clinical events is currently being assessed in an outcome trial of patients following an acute coronary syndrome.

The Primary Goal of Dyslipidemia Treatment in Patients with Diabetes

LDL-cholesterol

All major national organizations recommend that the primary goal of treatment in patients with diabetes should be an LDL-C <100 mg/dL. If cardiovascular disease is present, it is reasonable to aim for an LDL-C goal of <70 mg/dL (or a 50 % reduction in LDL cholesterol if baseline LDL-C is very high). If cardiovascular disease is not present, but the patient has multiple other cardiovascular risk factors, then a 30–40 % reduction in LDL-C, regardless of baseline levels, is appropriate.

Triglycerides

If triglycerides are >200 mg/dl after the LDL-C goal is achieved, non-HDL cholesterol should be set as a target of therapy (<130 mg/dl). For patients with diabetes and cardiovascular disease the optional goal is <100 mg/dl. Treatment options include using a higher dose of statin, fibrates, niacin or omega-3 fatty acids.

HDL-cholesterol

If triglycerides are <200 mg/dl, an additional treatment option should be considered. It can be difficult to raise low HDL-C levels. Glycemic control, statins and fibrates have small effects on HDL-C levels. Niacin is the most effective treatment for increasing HDL-C, but it may modestly impair glycemic control. The thiazolidinediones can increase HDL-C by about 5–10 %.

The impact of current and emerging therapies on the functionality, rather than absolute quantity, of circulating HDL-C remains to be determined.

Conclusions

Type 2 diabetes is increasing worldwide and is a significant risk factor for developing cardiovascular disease. A cluster of plasma lipid and lipoprotein abnormalities (low HDL-C, small dense LDL particles and elevated triglycerides) contributes to the risk of atherosclerosis and coronary heart disease in the majority of patients with type 2 diabetes. Statins are very efficacious in reducing cardiovascular risk in patients with type 2 diabetes and remain the mainstay of dyslipidemia management.

Despite optimal therapy to achieve LDL-C goals, many of these patients will not achieve all lipid targets—particularly for triglycerides, non-HDL-C and HDL-C—and will remain at high risk of cardiovascular events. Additional treatment, such as fibrate, niacin, ezetimibe or thiazolidindiones, therefore seems to be important to reduce residual risks. Ongoing trials with currently-available therapies are expected to provide some much-needed answers. ■

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