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Towards more specific treatment for diabetic dyslipidemia

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Abstract

Purpose of review—Treatment of diabetic dyslipidemia is necessary because of its impact on cardiovascular disease, which is the leading cause of death in patients with diabetes. In the past, standard treatment of diabetic dyslipidemia focused only on correcting lipids. Although this remains the mainstay of treatment, because new antihyperglycemic treatments reduce cardiovascular events with minimal effect on dyslipidemia, a new approach is both timely and relevant.

Recent findings—LDL-lowering remains the focus of treatment for diabetic dyslipidemia, especially in patients with both diabetes and cardiovascular disease (CVD). Higher intensity statin therapy or lower LDL cholesterol goals are recommended in these patients. Combination therapy, especially with ezetimibe, fibrates, bile acid sequestrants, PCSK9 inhibitors and omega 3 fatty acids should be considered along with selected new agents to reduce glycemia.

Summary—As diabetic dyslipidemia plays a key role in CVD, aggressive treatment is indicated. New research targets include apo-CIII and lipoprotein(a) [Lp(a)]. In addition, new antihyperglycemic therapy is changing diabetes care and altering treatment guidelines. The most recent American Diabetes Association Standards of Care has expanded its recommendations for people with CVD and diabetes, suggesting that medications validated to improve cardiac health should be strongly considered.

Keywords

cardiovascular disease; diabetic dyslipidemia; LDL; triglycerides

INTRODUCTION

When approaching treatment for patients with diabetes, cardiovascular disease (CVD) risk reduction has increasingly been in the forefront of therapeutic goals. There are several risk factors apart from hyper-glycemia that contribute to the high prevalence of CVD seen in patients with diabetes, with one of the most important being diabetic dyslipidemia [1,2].

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Conflicts of interest

There are no conflicts of interest.

DIABETIC DYSLIPIDEMIA

Diabetic dyslipidemia is characterized by a state of elevated triglycerides, small dense LDL particles, and low HDL cholesterol. The causes of small, dense LDL are disputed. Cholesteryl ester transfer protein (CETP)-mediated transfer of triglyceride from VLDL to LDL followed by lipolysis mediated by hepatic lipase creates smaller LDL. Other data suggest that normal hepatic function will secrete either a specific precursor or directly secrete these smaller LDL into the circulation. Other atherogenic lipoprotein particles, including VLDL and chylomicron remnant particles are also increased. In type II diabetes, this process is driven by insulin resistance, which causes a rise in free fatty acids in the serum, leading to increased chylomicron and VLDL production in both fasting and nonfasting states. In poorly controlled type I diabetes, insulin deficiency plays a similar role to increase fatty acid release from adipose tissue [2].

In addition to reducing the risk of pancreatitis secondary to hypertriglyceridemia, which sometimes accompanies diabetic dyslipidemia, the primary reason to treat diabetic dyslipidemia is to reduce CVD. Lifestyle modifications, including diet (caloric restriction to lose weight, reducing carbohydrates and avoidance of fats and alcohol that exacerbate hypertriglyceridemia), as well as increasing aerobic exercise, are considered the initial steps in managing diabetic dyslipidemia [3]. Most often, however, lipid-lowering pharmacotherapy is required to successfully normalize diabetic dyslipidemia. In fact, a recent meta-analysis of over-weight patients with type 2 diabetes mellitus showed that at least 5% weight loss was required to observe any, if only limited, improvements in lipid profile [4].

TARGETING LDL CHOLESTEROL WITH STATINS

LDL reduction with statin therapy has been and remains the mainstay of pharmacotherapy for diabetic dyslipidemia. Although studies have not shown any significant difference in the prevalence of elevated LDL cholesterol in individuals with diabetes compared with without diabetes [3], total LDL cholesterol may be a misleading measurement in diabetes. This may in part be because of the significant shift to small dense LDL in diabetic dyslipidemia, which is associated with greater CVD risk [5]. In effect, the same level of calculated LDL can be associated with greater plasma levels of apoB and, hence, more LDL particles. Whether having more particles with each particle having less cholesterol makes them more pathogenic is debatable.

What is certain is that the percentage reduction in LDL lowering is strongly correlated with reduction in atherosclerotic CVD (ASCVD) risk [6]. In addition, decreased cardiovascular morbidity and mortality with statin therapy outweigh the slight increased risk of developing diabetes, even when considering patients at high risk of developing diabetes [7,8].

The 2013 American Heart Association/American College of Cardiology guidelines for cholesterol management were groundbreaking and, in many ways, controversial in their shift from prioritizing cholesterol treatment targets to instead recognizing large groups of higher risk patients and using risk categories to determine therapy [9]. Nonetheless, several experts

still postulate that the lower the LDL the better, because of studies like Treating to New Targets (TNT), which compared CVD outcomes in patients treated with high-dose vs. low-dose atorvastatin therapy and reaching LDL 75 and 100 mg/dl, respectively. Though the composite primary outcome benefit was not driven by coronary artery disease (CAD) mortality, there was significant reduction in stroke [10]. Other studies, which examined statin benefit on CVD, such as the Heart Protection Study (HPS) and the Collaborative Atorvastatin Diabetes Study (CARDS), did not seem to show a threshold below which statin therapy ceased to be beneficial [11,12]. More recent trials using ezetimibe and PCSK9 inhibitors clearly show that greater LDL reduction on top of statin therapy provides added benefit, without attenuation in CVD benefit in patients starting treatment with lower LDL [13■■,14].

COMBINATION THERAPIES

Despite the tremendous benefits that statin therapies provide, one in seven patients with diabetes using statins will still eventually suffer a cardiovascular event over 5 years [6]; this emphasizes the need for new therapeutic agents. Combination therapy to achieve greater LDL lowering is becoming increasingly popular in the management of diabetic dyslipidemia; not only is there a potential for greater LDL lowering but also a reduction in other cholesterol subtypes, namely apoB, Lp(a) and triglycerides may contribute additional benefit [15].

One such add-on therapy that has shown enhanced LDL lowering benefit in patients with diabetes or at high risk for CVD, is ezetimibe. Ezetimibe blocks cholesterol absorption in the gut via the Niemann–Pick C1-like 1 (NPC1L1) protein, leading to LDL lowering. The IMPROVE-IT study showed that ezetimibe add-on therapy to simvastatin is particularly beneficial in patients with diabetes. Although the study population was composed of high-risk CVD patients with and without diabetes, the prespecified subgroup analysis of those with diabetes randomized to ezetimibe had a 14% relative risk reduction in cardiovascular events, in addition to an overall further 24% reduction in LDL, compared with diabetic participants receiving simvastatin alone. In comparison, nondiabetic participants in IMPROVE-IT had a smaller relative benefit with combination therapy of simvastatin with ezetimibe. It is unclear whether ezetimibe’s CVD benefit in patients with diabetes is a result of the additional LDL lowering alone, or whether some of its benefit may be derived from reduction in other non-HDL cholesterol [14].

PCSK-9 antibodies are promising new therapies that lower LDL- cholesterol by more than 50%; the degree of incremental LDL lowering remains despite concomitant statin therapy. They do this by allowing LDL receptor recycling, thereby increasing their availability to remove LDL from the serum [16]. Data from the FOURIER study is promising in confirming that additional LDL reduction with PCSK9 inhibition results in further CVD risk reduction, especially in patients with diabetes [13■■]. More recently, results from the ODYSSEY cardiovascular outcome trial (CVOT) support these findings, demonstrating a 3.4% absolute risk reduction in MACE in patients treated with PCSK-9 antibody to mean LDL of53.3 mg/dl, compared with LDL of 101.4 mg/dl in the placebo group [17]. Given their high cost and difficult insurance approval process [18], PCSK-9 antibody use is

currently limited to patients with heterozygous familial hypercholesterolemia who are statin intolerant, or who have clinical ASCVD requiring additional lowering of LDL. One interesting PCSK9 inhibitor effect that needs further investigation, and could broaden its role in dyslipidemia management, is its ability to lower Lp(a); the degree in lowering may vary from patient to patient [19]. This is significant considering that Lp(a) is an independent risk factor associated with increased atherogenesis, thrombosis and aortic stenosis. Whether treatments that lower Lp(a) levels will reduce CVD independent of their reductions in LDL levels is currently unknown and requires validation [20]. Clinical Lp(a) reduction trials using antisense oligo-nucleotides that lower apo(a) levels by nearly 90% are underway. For some patients with diabetes and increased Lp(a), such therapies may enter the clinic soon [21,22].

Hypertriglyceridemia is one of the primary characteristics of diabetic dyslipidemia, and unlike LDL cholesterol, triglyceride levels are significantly higher in patients with diabetes compared with patients without diabetes. However, the role of triglyceride lowering has been much more controversial than that of LDL, and to date, there is conflicting evidence with regards to its CVD benefits. Despite some inconsistencies, there are significant data pointing towards CVD benefit for the group of patients with especially elevated triglycerides (>200 mg/dl) and lower HDL levels (below 40 mg/dl) [23]. Fibrates are the most effective drugs in triglyceride lowering, acting as peroxisome proliferator-activated receptor (PPAR) alpha agonists to increase fatty acid oxidation [24]. In the FIELD trial, the cohort of patients using fenofibrate therapy with the higher triglycerides and lower HDL cholesterol did have a significant 27% reduction in cardiovascular death, myocardial infarction, stroke and need for coronary/carotid revascularization [25]. The post hoc ACCORD-Lipid trial showed similar CVD benefit when analyzing subgroup data [26]. However, drop-in use of statin therapy in the placebo group may have attenuated the potential benefit seen with fenofibrate use. Newer, more potent fibrate-like therapies, such as pemafibrate, are being studied in patients solely with diabetes and hypertriglyceridemia and will hopefully clarify triglyceride lowering and CVD benefit apart from that seen with statins [27].

Omega-3 fatty acids (OM3FA) have also been used as add-on therapy to help reduce triglycerides [28]. A recent meta-analysis demonstrated that omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events [29]; however, there are currently no published CVD outcome trials using these agents. Both the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) and Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh CV Risk PatienTs with Hypertriglyceridemia (STRENGTH) are underway and will hopefully help determine this class' position in diabetic dyslipidemia.

One of the older second-line therapies for diabetic dyslipidemia, nicotinic acid (niacin), is effective in lowering LDL as well as triglycerides; in addition, similar to PCSK9 inhibitors, this class has been shown to reduce Lp(a) levels by 15–30%, and some of this effect may be derived from niacin itself impacting PCSK9 as well [30]. Older trials that showed the efficacy of this treatment to reduce CVD events [31], used rapid release crystalline niacin; more recent trials have used slower release compounds that induce less flushing, uric acid elevation and liver function abnormalities. These recent trials have failed to show benefit in statin-treated individuals. In addition, niacin is still usually poorly tolerated because of

gastrointestinal side effects, making it less popular with patients [32,33]. Nonetheless for patients with very high LDL levels despite statin use, who are unable to use PCSK-9 inhibitors, niacin may still have a role. Of note, some prior trials with niacin may have not included the patients most likely to benefit from it, for example, the HPS-2 Thrive Study excluded patients with especially elevated LDL [33].

NOVEL TARGETS

Novel targets to reduce triglycerides and cholesterol are being investigated and provide an exciting new approach to diabetic dyslipidemia therapy. One such target is apo-CIII. Apo-CIII is thought to block lipoprotein lipase (LpL), the limiting enzyme for hydrolysis of circulating triglycerides, and increase VLDL uptake in the liver. After the discovery in 2008 of an apo-CIII null mutation associated with lower triglycerides and decreased CVD incidence, antisense therapies to apo-CIII have been developed, and so far, have shown very promising results. More than a 50% reduction in severe hypertriglyceridemia has been found with this therapy, which is even effective in patients with genetic LpL deficiency [34].

LpL is modulated by a series of inhibitors of the angiopoietin-like protein (Angptl) family. Angptl4 is the adipose tissue factor that allows more lipolysis during prandial periods and less LpL activity during fasting. Unfortunately, inhibition of this protein led to abdominal inflammation in animal models. Angplt3 is associated with hypobetalipoproteinemia, but with the development of fatty liver. Both antisense and antibodies against this protein reduce circulating LDL levels [35■■,36] and likely will also reduce triglyceride levels.

By contrast, raising HDL cholesterol with cholesteryl ester transfer protein (CETP) inhibitor therapies has not been shown to be effective in reducing diabetic dyslipidemia risk, and more recent genome wide association study studies do not support a strong association between HDL mutations and CVD [24,37,38]. Despite the lack of a primary outcome benefit with CETP inhibitors, a recent study showed that individuals taking anacetrapib had a reduction of major coronary events; this benefit was ascribed to the marked LDL reduction with this therapy and not changes in HDL [39■]. We cannot ignore that reduction in HDL remains part of the diabetic dyslipidemia phenotype. However, recent data suggests more research in improving HDL quality, as opposed to quantity, is needed.

ROLE OF GLUCOSE-LOWERING THERAPIES, OLD AND NEW

A reinvented approach to treating diabetic dyslipidemia is considering using drugs that not only lower cholesterol but also lower blood sugar. Bile acid sequestrants are one of the medications to lower LDL cholesterol and reduce CVD. However, use of these medications markedly diminished with the advent of statin therapy, largely because of their adverse gastrointestinal side effects and inferiority in degree of LDL lowering. The newer generation bile acid sequestrant, colesevelam, which is generally better tolerated, may be reconsidered as add-on therapy to statins, or for patients with statin intolerance. Although no CVOTs are currently available for this drug, it has the additional advantage of improving HbA1C, though like all bile acid sequestrants, this drug will increase triglyceride levels in many patients [40].

Studies in patients with diabetes have led the way to show that nonlipid reducing therapies will reduce CVD. Considering how central insulin resistance is in the pathophysiology of diabetic dyslipidemia in type 2 diabetes especially, it is not surprising that, pioglitazone, one of the most potent insulin sensitizers should be strongly considered as part of treatment. Pioglitazone is thought to have a fibrate-like action to reduce liver production of apo-CIII and increase LpL activity leading to more rapid clearance of circulating VLDL [41]. Though not approved for treatment of diabetic dyslipidemia specifically, its mechanism of action, in addition to its recent use in reducing stroke recurrence, makes this a promising future adjunctive therapy in certain patients with diabetes [42]. Prior studies in rodents had suggested that PPARg agonists would reduce atherosclerosis either because of direct vascular effects or because of reduced macrophage inflammation [43].

Other glucose-lowering therapies, such as SGLT-2 inhibitors and GLP-1 agonists have cardiovascular risk-lowering capabilities [44,45] that appear to be exclusive of any effects on dyslipidemia. In some studies, SGLT2 inhibitors had modest triglyceride-lowering effects, but also minimally increased both LDL and HDL cholesterol levels. The reason for these changes in lipoprotein profiles is not completely understood. By contrast, in some larger trials, no significant changes in circulating lipoproteins were found [46]. Unfortunately, data specifically analyzing patients with hypertriglyceridemia is not yet available and should be investigated.

GLP-1 receptor agonists also reduce CVD events, although they also impact diabetic dyslipidemia. In part, this might be because of the weight reduction that occurs with these agents; GLP-1 agonists impact weight more significantly than SGLT2 inhibitors. Data supports a role for these drugs to reduce hepatic VLDL production and de novo lipogenesis [47].

DDP4 inhibitor effects on dyslipidemia are also being reexamined. Though lipid lowering has not been shown to be a class effect, one agent of interest is anagliptin, which is thought to have inhibitory effects on hepatic cholesterol synthesis. Recently, a phase III trial demonstrated reduced LDL cholesterol by 9.5 mg/dl over 12 weeks, regardless of the use of statins [48]. Though CVOTs to date have not demonstrated significant cardiovascular benefit with use of these agents, more research is warranted.

CONCLUSION

It is important to recognize that the primary goal of treating diabetic dyslipidemia is to reduce CVD, and that dyslipidemia is just one of the several risk factors that contributes to CVD in patients with diabetes. Though LDL lowering with statin therapy remains the mainstay of diabetic dyslipidemia treatment, combination therapy with niacin and fibrates can be considered, but should be used with caution[49]. Specific populations who may receive benefit from additional therapies include those with especially elevated LDL and/or triglycerides. In addition, the role of PCSK9 inhibitors, omega 3 fatty acids and selective antisense oligonucleotides to apo-CIII and Angptl3 may be expanding in the future. Finally, as the focus of diabetic dyslipidemia is to lower CVD risk, newer antihyperglycemic medications proven to lower cardiovascular morbidity and mortality, such as SGLT-2

inhibitors and GLP-1 agonists, should be emphasized [50■], particular for diabetic patients with established CVD. Future studies with these agents and with pioglitazone have shown that CVD treatment is more than reduction in circulating lipids. Understanding the reasons for the clinical benefits of these agents will illustrate important targets to prevent and treat cardiovascular complications of diabetes.

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KEY POINTS

- LDL lowering remains the cornerstone of treatment for diabetic dyslipidemia.
- Combination therapies for optimizing the cholesterol profile are an increasingly used option for treatment of diabetic dyslipidemia.
- Lifestyle changes remain an important component of treatment of diabetic dyslipidemia.
- Novel targets to reduce triglycerides are under investigation, and hold promise in treatment of diabetic dyslipidemia.
- New glucose-lowering therapies that reduce cardiovascular disease are of growing importance in the treatment of diabetes.