Dyslipidemia in diabetes mellitus and cardiovascular disease

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Patients with diabetes have a high residual risk for cardiovascular disease (CVD) and adverse outcomes despite statin therapy and lifestyle modifications. Particular to individuals with diabetes is the pattern of elevated triglycerides, small dense low density lipoprotein cholesterol, and reduced levels of high density lipoprotein cholesterol, described as dyslipidemia of diabetes. The role of combination therapy with an additional agent such as niacin, ezetimibe, fenofibrate, and n-3 fatty acids has been studied; however, at the same time, these agents have come under criticism for their limitations. We performed a review of key trials assessing the benefit of combination therapy to reduce CVD risk from dyslipidemia. Of the currently available agents that can be used in combination with statins, ezetimibe has the most favorable risk profile, with a recent trial demonstrating modest incremental

benefit when given in addition to statins. PCSK9 inhibitors are a promising category, although clinical outcome data in individuals with diabetes are pending. *Cardiovasc Endocrinol* 6:27–32 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

The burden of cardiovascular disease (CVD), the major cause of morbidity and mortality around the world [1], is particularly high among patients with type 2 diabetes mellitus (T2DM) [2,3], with the proportion of CVD attributable to diabetes increasing in the general population [4]. With the prevalence of diabetes itself rising, particularly among ethnic minorities, CVD risk reduction in this population is of great public health importance [5]. Although lifestyle modifications and statins are the first-line interventions for CVD risk reduction in individuals with diabetes [6], they remain at considerable risk for adverse cardiovascular events [7,8].

In this narrative review, we review the pathophysiology of dyslipidemia in individuals with diabetes and summarize the key trials that report on cardiovascular risk reduction in these patients. We conclude by summarizing the positions of major professional bodies on the management of dyslipidemia in individuals with diabetes and conclude by presenting recommendations for future research in this area.

Mechanisms of dyslipidemia in individuals with diabetes

Patients with diabetes are at an elevated risk for adverse cardiovascular outcomes compared with controls [9,10]. Although in nondiabetic individuals LDL is predictive of cardiovascular outcomes [11], the prevalence of LDL is similar between individuals with diabetes and non-diabetic individuals [12,13], and data suggest that the elevated risk for CVD in individuals with diabetes occurs

independently of the serum LDL level [14]. The pattern of dyslipidemia usually presents with elevated triglycerides and small dense LDL and reduced levels of high density lipoprotein cholesterol (HDL-C) [15]. Increased LDL particle numbers from either elevated ApoB or LDL-P are a prominent feature of dyslipidemia in diabetes. Small dense LDL particles are more atherogenic and are associated with a higher rate of nephropathy [16]. Individuals with diabetes have also been noted to have lower HDL levels [17].

Insulin resistance is the primary mechanism leading to lipid derangements in individuals with diabetes [18]. Peripheral resistance to insulin increases the release of free fatty acids from adipose tissue, which are taken up by the liver; increased hepatic uptake of free fatty acids leads to more synthesis of triglycerides. Triglyceride synthesis subsequently stimulates hepatic production of triglyceride-rich very low density lipoprotein cholesterol (VLDL) and increased secretion of ApoB [19]. Triglyceride-laden VLDL enrich LDL and HDL through the action of the cholesterol ester transfer protein, making them more cholesterol rich [20]. These triglyceride-rich LDL molecules are then hydrolyzed by hepatic or lipoprotein lipase leading to the production of small dense LDL.

Therefore, the lipid derangements associated with diabetes are widespread, beyond just LDL elevation, making it challenging to rely on conventional means for cardiovascular risk reduction.

Lifestyle modifications: diet and exercise

Lifestyle modification in individuals with diabetes pertains to dietary restriction and physical exercise. Dietary restriction's benefit is realized through weight loss. In this regard, caloric restriction is essential and any degree of weight loss is beneficial. In a randomized study, caloric restriction led to improvements in all markers, including glycemic control, HbA1c, and lipid profile, in obese and overweight individuals with diabetes [21]. It remains unclear, however, as to what type of dietary modification is best for individuals with diabetes. Although both the American Diabetic Association [22] and the Adult Treatment Panel III guidelines [23] recommend a diet low in monosaturated fats, recent data support a low-carbohydrate diet. A trial in Spain randomizing patients to a fat-rich Mediterranean diet showed a significant reduction in cardiovascular events [24] and a lower incidence of diabetes compared with patients advised a low-fat diet [25]. However, despite dietary modification improving some measures, no mortality benefit has yet been demonstrated in diabetic patients. One multicenter randomized controlled trial (Look Action for Health in Diabetes), which randomized overweight and obese individuals with diabetes to either caloric restriction and physical exercise or usual care, resulted in improvement in obesity, but was unable to show improvement in lipid profiles, cardiovascular events, or mortality [26]. Similar to diet, exercise has been shown to result in better glycemic control [27] and lipid profiles [28–30]; no reduction in cardiovascular events or mortality has ever been shown.

Statin therapy

Statins are the first-line treatment for hyperlipidemia in all patients, including those with diabetes, and have the strongest evidence base of any intervention in patients with or without diabetes [31]. The benefits of statins increase with dose intensity [32] and are independent of the patient's initial lipid profile, as demonstrated in the CARDS trial [33,34]. The cardiovascular risk reduction that individuals with diabetes accrue is independent of their individualized risk for future events [35].

One concern about statin use has been the increased incidence of T2DM in patients taking statins [36]. In one trial, 270 patients on rosuvastatin developed diabetes versus 216 on placebo [37]. The small increase in incidence is offset by the benefits of statin therapy. One meta-analysis showed that one of 255 patients would develop diabetes after being treated with statins for 4 years, most of whom were prediabetic; however, in this same cohort, 5.4 vascular events were prevented [38].

Residual risk in individuals with diabetes

There remains residual risk for CVD with all monotherapies, despite intensification of statins. Implementation of lifestyle modifications and the institution of statin

therapy still leave patients with T2DM with a substantial risk for future CVD [39]. One of seven individuals with diabetes on statins experience major adverse cardiovascular events within 5 years [31]. In one trial, despite a multi-dimensional approach, 50% of patients went on to have microvascular complications from dyslipidemia [40]. Although agents including ezetimibe, fibrates, niacin, and n-3 fatty acids have been used, they have no established role as monotherapy in statin-tolerant patients [41].

Combination therapy: a review of key clinical trials

The role of monotherapy with a nonstatin agent is only indicated in patients who are statin-intolerant. The role, if any, of adding a medication to supplement statin risk reduction has been extensively studied and here we summarize key clinical trials by pharmacologic category.

Ezetimibe

Ezetimibe is a cholesterol absorption inhibitor that reduces uptake from the intestine while also increasing the breakdown of LDL. Ezetimibe has been extensively tested in combination with statins (Table 1).

Many trials show improved lipid profile with the addition of ezetimibe to statins. In EASE, patients with at-goal LDL levels were randomized 2 : 1 to receive ezetimibe or placebo in combination with a statin and were found to have better LDL control after 6 weeks of treatment [42]. In VYTAL, 1229 individuals with diabetes were randomized for 6 months to receive ezetimibe and simvastatin or atorvastatin alone, with the ezetimibe/simvastatin combination demonstrating better lipid profiles [43]. In ENHANCE, 720 patients with familial hypercholesterolemia receiving simvastatin were randomized to receive ezetimibe or placebo and found that, although LDL was lower, there was no difference in CIMT in the combination group [44]. A substudy of SANDS, which randomized 499 diabetic patients with intensive lipid and blood pressure control or conventional control for 3 years, showed no additional benefit when ezetimibe was added to statin therapy with regard to CIMT regression or LDL. [45]. ARBITER 6-HALTS analyzed the addition of niacin or ezetimibe to ongoing statin therapy and showed greater CIMT regression and lower cardiovascular events (1 vs. 5%, $P=0.04$) with niacin compared with ezetimibe [46].

IMPROVE-IT was a double-blind trial enrolling 18 144 high-risk patients within 10 days of an acute coronary syndrome, which randomized patients to receive simvastatin and ezetimibe or simvastatin and placebo with an LDL less than 125 mg/dl. The trial demonstrated a 6.4% relative risk reduction in the primary endpoint, which was a composite of cardiovascular death, myocardial infarction (MI), hospital admission for unstable angina, coronary revascularization more than a month after randomization, and stroke [47]. Results in the prespecified diabetic subpopulation were presented at the European

Table 1 Key clinical trials analyzing combination of ezetimibe and statins

Ezetimibe			
Trials	Designs	Results	Additional findings
EASE, 2005, statin and ezetimibe vs. statin and placebo [42]	3030 patients with LDL exceeding ATP III goal, randomized 2 : 1 to ezetimibe or placebo for 6 weeks	LDL control better with combination (71 vs. 21%, $P < 0.05$); improvement in CRP also noted	Ezetimibe found to be beneficial to reach lower LDL level when added to statin therapy
VYTAL, 2006, ezetimibe and simvastatin vs. atorvastatin [43]	1229 adults with type 2 diabetes randomized for ~6 months	LDL better controlled with combination compared with atorvastatin alone with similar risk profile	Simvastatin and ezetimibe combination had better lipid profile compared with atorvastatin alone
ENHANCE, 2008, simvastatin 80 mg with ezetimibe vs. simvastatin 80 mg alone [44]	720 patients with familial hypercholesterolemia randomized in a double-blind study over 24 months	No difference in CIMT; LDL lower 16% in the combination group	No difference in adverse effects between the two groups
SANDS, 2008, simvastatin and ezetimibe vs. simvastatin alone (LDL goal < 70 mg/dl, SBP < 115 mmHg) vs. statin alone (conventional arm) [45]	499 individuals with diabetes > 40 years of age without CVD randomized to aggressive LDL, SBP arm, and conventional arm (LDL goal < 100 mg/dl, SBP < 130) over 3 years	No difference in LDL lowering and CIMT regression in the statin alone vs. the combination group in aggressive arm	CIMT and left ventricular mass regressed greater in aggressive arm but no difference in clinical events between conventional and aggressive arms
ARBITER 6-HALTS, 2009, extended release niacin and statin vs. ezetimibe and statin [46]	208 patients with CVD with LDL < 100 mg/dl and HDL < 50–55 mg/dl; terminated early after 14 months on the basis of efficacy	Greater CIMT regression and lower cardiovascular events (1 vs. 5%, $P = 0.04$) with niacin compared with ezetimibe	Greater LDL reductions with ezetimibe were paradoxically associated with an increase in CIMT
IMPROVE-IT, 2014, ezetimibe and simvastatin 40 mg vs. simvastatin 40 mg alone [47]	18 144 moderate-high risk patients post acute coronary syndrome with LDL < 125 mg/dl (statin naive) or and > 79 mg/dl over 5.7 years	Absolute risk reduction of 2.0% in primary endpoint with the addition of ezetimibe. Greater LDL reductions also noted in the ezetimibe arm	Greater LDL reductions were associated with improved outcomes. 10% reduction in cardiovascular death, nonfatal MI or nonfatal stroke but not all-cause mortality

CIMT, carotid intima-media thickness; CRP, C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure.

Society of Cardiology conference, which showed a 14% relative risk reduction over placebo in the ezetimibe arm compared with 2% for nondiabetic individuals for major adverse cardiovascular outcomes [48]. Although the manuscript has not yet been published, these results suggest that ezetimibe may have a future possible role as an agent for treating diabetic dyslipidemia in combination with statins.

Fibrates

Fibrates enhance ApoA1 synthesis, resulting in increased levels of HDL and also reduce hepatic triglyceride production [49]. In a placebo-controlled trial, fenofibrate resulted in a significant reduction in nonfatal MIs and revascularization in individuals with diabetes [50]. This benefit was not realized when fibrates were administered in combination with statins. In the ACCORD trial, which randomized 5518 patients on statin therapy to addition of fenofibrate or placebo, there was no reduction in cardiovascular events [51]. However, in the prespecified group with high triglycerides and low HDL, there was a reduction in clinical events that approached significance (12.4 vs. 17.3%, $P = 0.057$); a subsequent meta-analysis showed a reduction in cardiovascular events in this high triglycerides and low HDL-C diabetic population [52].

N-3 fatty acid ethyl esters

The addition of n-3 fatty acids has been analyzed in two randomized clinical trials. The JELIS trial randomized 18 645 Japanese patients on statins with total cholesterol

more than 6.5 mmol/l to eicosapentaic acid versus placebo. These patients were followed up for a mean of 4.6 years. This trial demonstrated fewer adverse cardiovascular events in patients with known coronary artery disease (8.7 vs. 10.7%, $P = 0.01$) but not in those without [53]. Another RCT randomized 188 patients without prior CAD on simvastatin, with triglycerides between 200 and 500 mg/dl and tight LDL control, to omega-3-acid ethyl esters versus placebo. Although a reduction in HDL was noted, no improvement was noted in clinical events [54].

Niacin

Niacin, a nicotinic acid derivative, slows the hepatic uptake of HDL by downregulating hepatic HDL-ApoA1 receptors and increases HDL production. Clinical studies have demonstrated that niacin produces a very robust increase in serum HDL [55] more so than even statins in one study [56]. However, success in improving clinical outcomes in combination with statins has not been demonstrated (Table 2). The combination of niacin with a statin was compared with statin in placebo in ARBITER 2 showing an improvement in HDL but none in CIMT regression [57]. ARBITER 3, however, did show a difference in CIMT regression between the niacin-statin group and the statin-placebo group [58]. Similarly, patients treated with niacin-statin in the OXFORD-NIASPAN study showed a greater reduction in carotid wall area on magnetic resonance imaging compared with the statin-placebo group [62].

Table 2 Key clinical trials analyzing combination of statins and niacin

Niacin			
Trials	Designs	Results	Additional findings
ARBITER 2, 2004, extended release niacin and statin vs. statin and placebo [57]	167 patients with CAD, HDL < 45 mg/dl randomly assigned in a double-blind study	HDL increased 21% in the niacin group; no change in CIMT progression after 1 year	CIMT progression slower on niacin in patients with insulin resistance ($P = 0.026$)
ARBITER 3, 2006, extended release niacin and statin vs. statin and placebo [58]	130 patients with CAD, HDL < 45 mg/dl randomly assigned in a double-blind study who completed ARBITER 2	9 mg/dl increase in HDL; net regression noted in CIMT regression (-0.041 mm, $P < 0.05$)	Changes in HDL associated with CIMT regression after multivariate analysis
OXFORD NIASPAN, 2009, high-dose niacin and statin vs. statin and placebo	71 patients with HDL < 40 mg/dl randomly assigned in a double-blind study followed up for 12 months	Carotid wall area on MRI was significantly reduced in the niacin group (-1.1 vs. $+1.2$ mm, $P < 0.05$)	The niacin group also had higher HDL compared with placebo
AIM HIGH, 2011, extended release niacin vs. placebo in patients on simvastatin with ezetimibe for LDL < 70 mg/dl [59]	3414 patients with CVD; trial stopped after a mean of 3 years for lack of clinical efficacy; 34% individuals with diabetes	No difference in clinical endpoints with niacin despite improved lipid profile; post-hoc trend toward benefit in lowest HDL, highest TG group ($P = 0.07$) [60]	Niacin also noted to increase the rate of serious infections and gastrointestinal disorders in subsequent analysis
HPS2 Thrive, 2014, extended release niacin-laropiprant (tredaptive) vs. placebo in patients on statins [61]	25 673 patients with vascular disease; followed up for a median of 3.9 years; 32% individuals with diabetes	No clinical benefit with niacin; significant increase in diabetes, diabetic disturbances and other adverse events	Merck withdrew tredaptive from market; future role of niacin in the treatment of hyperlipidemia questionable

CAD, coronary artery disease; CIMT, carotid intima media thickness; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglyceride.

AIM-HIGH randomized 3414 patients with known CVD to extended release niacin or placebo [59]. This trial was stopped after 3 years due to lack of clinical efficacy and an increase in serious infections and gastrointestinal disorders. Results from HPS-2 Thrive, in which 25 673 patients were randomized to extended release niacin-laropiprant versus placebo in patients on statins and tight LDL control, were similarly disappointing [61]. Not only was there an absence of any clinical benefit with niacin after 3.9 years of median follow-up but also a wide array of serious adverse effects including new onset diabetes and worsening of pre-existing diabetes was noted. The manufacturer removed this compound from the market after these results were released. Results from either trial did not show any difference based on the presence of diabetes. Although a post-hoc analysis of AIM-HIGH suggested that patients with high triglycerides and low HDL demonstrated a trend toward possible benefit [60], given a negative result and a wide array of serious adverse events, there appears to be no role at present for niacin in statin-tolerant patients.

Guideline positions

The recent American Heart Association/American College of Cardiology guidelines for cholesterol management have rightly made statins the cornerstone for dyslipidemia management [63]. They recommend that diabetes be treated with statins if patients are between 40 and 75 years of age. If the diabetic patient's 10-year atherosclerotic CVD risk is at least 7.5% based on the pooled cohort risk calculator, a high-intensity statin such as atorvastatin 80 mg or rosuvastatin 40 mg is recommended. However, the guidelines authors have clarified subsequently that 'clinicians treating high-risk patients who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity

of a statin, or who are completely statin intolerant may consider the addition of a nonstatin cholesterol-lowering therapy' [64]. They denoted that individuals with diabetes between 40 and 75 years of age were in the high-risk group and pointed to ezetimibe as a potential option in this situation (IMPROVE-IT had not been published at the time the guidelines were published) [64]. Additional guidelines have also been published by other established organizations such as the American Diabetes Association, the European Society of Cardiology, the National Lipid Association, and the National Clinical Guideline Center in the UK [65]. Subtle differences in the guidelines pertain to risk stratification of patients and use of lipid targets for tailored and targeted therapy. Although most organizations do not make a specific recommendation for combination therapy, the European Society of Cardiology guidelines did indicate that ezetimibe may be added to statins after intensification of statin therapy in individuals with diabetes (level of evidence IIa) [66]. However, the Food and Drug Administration refused to approve ezetimibe as combination therapy citing modest benefit, missing data in the ezetimibe arm, and questioning the relevance of the reduction in nonfatal strokes and MIs that drove the risk reduction seen in the intervention arm.

Promising agents: ezetimibe and PCSK9 inhibitors

Despite the plethora of research in this area, the role of combination therapy in diabetic dyslipidemia remains controversial. However, the favorable results of the IMPROVE-IT trial may point to a role of ezetimibe as an adjunct to statin therapy, particularly if results are similarly positive in the diabetic subpopulation. PCSK-9 inhibitors, of whom Alirocumab (Regeneron Pharmaceuticals Inc., Eastview, New York, USA) and Evolocumab (Amgen Inc., Thousand Oaks, California, USA) have been approved,

have emerged as a category that has shown significant reductions in LDL [67]. A recent meta-analysis of three 12-week trials showed significant LDL lowering in individuals with diabetes [68]. However, data assessing clinical outcomes in individuals with diabetes remains scant and are being investigated in ongoing trials such as FOURIER (NCT01764633), ODYSSEY (NCT01663402), SPIRE-1 (NCT01975389), and SPIRE-2 (NCT01975376). However, at present there is no approved role for PCSK9 inhibitors specific to individuals with diabetes, although this is a rapidly evolving field [69].

For now, statins remain the mainstay of therapy in patients with dyslipidemia of diabetes with the role of combination therapy as yet unknown. Although there currently is an abundance of lipid-modifying options available for the reduction of lipid-related residual risk (i.e. elevated LDL-C, non-HDL-C, ApoB, and LDL-P) in the clinical setting of primary and secondary prevention of ASCVD, there is a dearth of appropriately designed clinical trials to enhance the desirable level of evidence 1A for combination studies. Studies with statins combined with fibrates and omega-3 FAs are recruiting or ongoing and additional information is still required about the impact of their addition to statin therapy. We await the results of the ongoing trials with PCSK9 inhibitors.

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Conflicts of interest

Jamal S. Rana received Institutional research grant from Regeneron and Sanofi. For the remaining author there are no conflicts of interest.

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