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Lipids and lipid management in diabetes



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Cardiovascular disease is more prevalent in type 1 and type 2 diabetes, and continues to be the leading cause of death among adults with diabetes. Although atherosclerotic vascular disease has a multi-factorial etiology, disorders of lipid metabolism play a central role. The coexistence of diabetes with other risk factors, in particular with dyslipidemia, further increases cardiovascular disease risk. A characteristic pattern, termed diabetic dyslipidemia, consists of increased levels of triglycerides, low levels of high density lipoprotein cholesterol, and postprandial lipemia, and is mostly seen in patients with type 2 diabetes or metabolic syndrome.

This review summarizes the trends in the prevalence of lipid disorders in diabetes, advances in the mechanisms contributing to diabetic dyslipidemia, and current evidence regarding appropriate therapeutic recommendations.

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Introduction

Diabetes mellitus contributes substantially to the global burden of disease, with an estimated 366 million people affected worldwide, and expected to increase to 552 million by 2030 [1].

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Cardiovascular disease (CVD) is more prevalent in patients with diabetes and is the leading cause of death among adults with diabetes [2,3]. Atherosclerotic vascular disease has a multi-factorial etiology that includes hypertension, hyperlipidemia, diabetes, obesity, chronic inflammation, sedentary lifestyle and cigarettes smoking [4]. In the absence of diabetes, disorders of lipid metabolism play a central role in atherogenesis and its progression [5,6]. In the Multiple Risk Factor Intervention Trial (MRFIT) study, among 340,000 middle-aged Americans, 1 mmol/L lower total cholesterol was associated with approximately 50% lower coronary disease risk [7]. Similar observations were reported in the Framingham cohort [8].

It had been shown that the presence of diabetes confers an enhanced CVD risk when compared with other traditional risk factors, in particular the association with dyslipidemia [9]. Patients with diabetes, especially type 2 diabetes (T2D), have an increased prevalence of lipid abnormalities, contributing to their high risk of CVD. More recent studies have reported that the prevalence of lipid disorders is much higher in children and youth with diabetes [10].

Multiple clinical trials have demonstrated favorable effects of pharmacologic (primarily statin) therapy on CVD outcomes in subjects with coronary heart disease (CHD) and for primary CVD prevention. Other classes of lipid lowering medication have shown less consistent effects on cardiovascular outcomes, in spite of their effectiveness on lipid levels.

This review summarizes the trends in the prevalence of lipid disorders in diabetes, advances in the mechanisms contributing to diabetic dyslipidemia, and current evidence regarding appropriate therapeutic recommendations.

Patterns and prevalence of dyslipidemia in diabetes

Although the prevalence of dyslipidemia is higher in T2D, various abnormalities of lipoprotein metabolism may also occur in individuals with type 1 diabetes (T1D) [11].

Patients with poorly controlled T1D present with elevated levels of triglyceride (TG)-rich lipoproteins [very low density lipoproteins (VLDL) and chylomicrons] due to a reduction in the activity of lipoprotein lipase (LPL) in the muscle and adipocytes [12]. This increase in TG-rich lipoproteins promotes an increased exchange of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesteryl esters for TG in chylomicrons and VLDL, which in turn reduces HDL-C levels and generates small, dense LDL [12]. Insulin deficiency is also associated with an increase in the absolute levels of LDL-C, LDL particle number, and apolipoprotein B-100, because LDL receptor expression is regulated, in part, by insulin. In contrast, patients who have well-controlled T1D have serum lipids and lipoprotein levels that are similar to those in the general population [11]. It has been reported that even when the absolute levels of plasma lipid and lipoprotein are normal, the apolipoprotein (apo) B-lipoproteins are cholesteryl ester-enriched and potentially more atherogenic [12]. In addition, the current weight trends in individuals with T1D, show an increased prevalence of obesity, metabolic syndrome [13,14], and as a consequence insulin resistance. These T1D individuals may present with dyslipidemia that resembles the characteristic abnormalities seen in patients who have T2D.

Most patients with T2D present with a cluster of lipoprotein abnormalities that include elevated fasting and postprandial TG levels, and decreased HDL-cholesterol levels. The levels of total and LDL-cholesterol are usually not significantly different in T2D patients compared with nondiabetic individuals, although some studies have reported that women with T2D may have a modest increase in LDL-cholesterol [15]. In the Framingham Heart Study, 13% of men and 24% of women with diabetes had increased total plasma cholesterol levels, compared with 14% of men and 21% of women without diabetes, while the prevalence of high LDL-cholesterol levels was 9% and 15%, respectively in men and women with diabetes mellitus compared with 11% and 16%, respectively in non-diabetic men and women [16]. The prevalence of high plasma TG levels (defined in this study as ≥ 2.65 mmol/L or 234.7 mg/dl) (19% men; 17% in women), and low HDL-cholesterol level (defined as ≤ 0.8 mmol/L or 30.93 mg/dl) (21% men and 25% women), were however significantly higher in individuals with diabetes than in those without diabetes (9% of men; 8% of women, and 12% men; 10% women, respectively) [16].

In spite of relatively normal absolute LDL-cholesterol levels, individuals with T2D usually present with an increase in the smaller, and more dense LDL particles. An increase in small LDL particle

cholesterol was reported by some to be associated with increased atherogenicity in diabetes [17,18], but other studies did not confirm this finding [19]. This dyslipidemia phenotype among T2D is not usually fully corrected with improvement of glycemic control, and is often found in insulin-resistant prediabetic subjects [20].

Lastly, in diabetes, lipid levels may be affected by factors unrelated to glycemia or insulin resistance, such as renal disease, hypothyroidism, alcohol or estrogen use, and genetically determined lipoprotein disorders (e.g., familial combined hyperlipidemia and familial hypertriglyceridemia).

Mechanisms of diabetic dyslipidemia

The pathophysiology of diabetic dyslipidemia is intricate and not fully understood. A detailed description of the complex pathways regulating the lipoproteins metabolism is beyond the scope of this work, and was amply discussed in [12,2].

Briefly, changes in plasma lipoproteins among patients with diabetes in the fasting and postprandial states are modulated by defects in insulin action and hyperglycemia [21]. In the postprandial state, dietary fatty acids (FA) and cholesterol absorbed by the intestinal cells are incorporated as TG and cholesteryl esters into chylomicrons, large particles that are mainly TG by weight. In the capillary beds of adipocytes (especially in the fed state) and muscle, chylomicrons are substrate for LPL which promotes lipolysis of chylomicrons TG and the release of FA. Insulin regulates LPL activity at several levels, including gene expression, protein synthesis, and secretion, and LPL is reduced in insulin-resistant individuals with T2D [22] with a consequent increase in plasma TG and decrease in HDL-C.

Alternatively, the obesity/insulin-resistant metabolic disarray may lead to lipid abnormalities independently of hyperglycemia. Recent evidence indicates that individuals with insulin resistance present with overproduction of ApoC-III, VLDL and ApoB-100, which further impairs LPL [23]. Fig. 1 summarizes most important pathways and their interactions in the presence of absolute or relative insulin deficiency. In the presence of insulin resistance, there is an increased flux of nonesterified fatty acids (NEFAs) from visceral adipose tissue which further reduce LPL activity, and stimulates overproduction of large VLDL particles by the liver, which, together with the chylomicrons absorbed from the gut, saturate the activity of LPL. These in turn contribute to producing prolonged postprandial lipemia, a common finding in individuals with insulin resistance. Since VLDL and chylomicrons compete for the same LPL-mediated pathway for TG removal from the circulation, postprandial hyperlipidemia may lead to inefficient VLDL and TG clearance. The generation of the small, dense LDL in insulin resistance is mainly modulated by the action of cholesteryl-ester-transfer-protein (CETP), which mediates the exchange of VLDL (or chylomicron) for LDL cholesteryl esters, thereby creating TG-enriched, cholesteryl ester-depleted LDL particles, which are lipolyzed by LPL or hepatic lipase, generating small, dense LDL. Small dense LDL is present in insulin-resistant/T2D patients, even in the presence of relatively normal TG levels [24].

In addition, an increased de novo hepatic lipogenesis, VLDL and TG, was described in obesity and insulin resistance further contributing to lipoprotein abnormalities [25,26].

Other characteristic features of T2D/insulin resistance are reduced levels of HDL-cholesterol and apoA-I, consequence of CETP action, increased hepatic lipase activity, and increased hydrolysis of TG and generation of smaller HDL [12]. The smaller, and more dense HDL particles are cleared more rapidly by the liver than intermediate and large size HDL, further contributing to decreased HDL-cholesterol and apo A-1 levels.

T1D provides a much clearer understanding of the relationship among diabetes, insulin deficiency, and lipid/lipoprotein metabolism. In poorly controlled T1D and ketoacidosis, hypertriglyceridemia and reduced HDL-C commonly occur. Insulin replacement in these patients corrects these abnormalities, and well controlled diabetics usually have increased HDL-C and lower than average TG levels.

Diabetic dyslipidemia and cardiovascular disease

Although the link between diabetes and atherosclerosis is not yet fully elucidated, experimental and epidemiological evidence suggest that diabetes may promote an earlier and more severe atherosclerotic vascular disease. For instance, approximately 30–40% of patients with acute coronary syndromes

have diabetes or metabolic syndrome, a prediabetic state, and in many instances the diabetes diagnosis is unveiled at the time of presentation [27]. Patients with diabetes and/or metabolic syndrome have an increased risk of recurrent cardiovascular events following an acute myocardial infarction (MI) [28–30]. Decrease in cardiovascular morbidity and mortality in people with diabetes is lagging behind to that of the general population [31,3].

Studies performed in various animal models aiming to understand the intricate relationship between diabetes, dyslipidemia and macrovascular disease reported inconsistent results. Diabetic mice deficient in apoE, a well-defined mouse model of atherosclerosis, presented with increased lesions' size compared with nondiabetic mice, an effect that was inhibited by the infusion of soluble fragments of the receptor for advanced glycosylation end products [32]. However, in these mice diabetes markedly increased circulating cholesterol levels. Data obtained in other animal models of atherosclerosis, such as the LDL receptor knockout mice or human apo B transgenic mice did not find more atherosclerosis in diabetic mice than control mice [33]. One can argue that there are important limitations in translating findings from mouse models to the human disease. However, very few studies were performed to date in larger animal models. One such study reported that alloxan-treated pigs develop increased atherosclerosis at increased rates once they become diabetics, although the plasma LDL-C was also more than doubled by diabetes [34].

These inconsistencies suggest that diabetes-mediated acceleration of macrovascular disease requires additional factors. One such factor is diabetic dyslipidemia.

Epidemiological data obtained in human studies found that, coexistence of diabetes with other risk factors, but in particular with dyslipidemia, confers a much greater CVD risk than either risk factor alone. MRFIT reported that among the 5000 men who had diabetes at baseline, the absolute risk of coronary mortality at each level of blood cholesterol (for 20 mg/dl increments in total cholesterol starting from 180 mg/dl to > 280 mg/dl), was 3–5 times higher in the presence of diabetes [7]. The United Kingdom Prospective Diabetes Study (UKPDS) has provided further evidence of a similar direct, and continuous, association of coronary disease risk with LDL- cholesterol concentration. Among ~3000 individuals with newly diagnosed T2D a 1 mmol/L increase in LDL-cholesterol was associated with a 57% increased risk of MI [35].

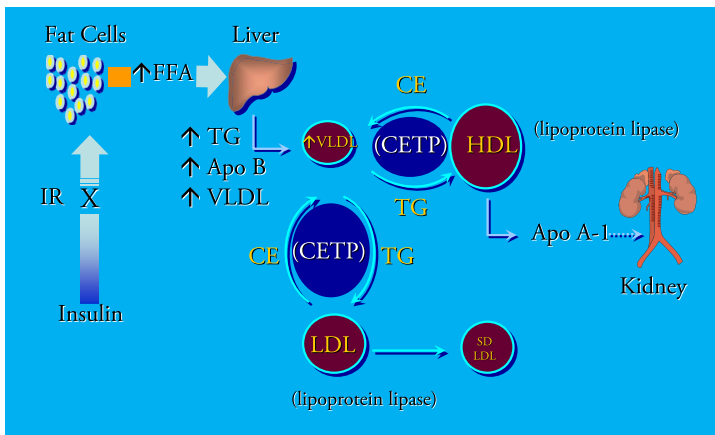


Fig. 1. Mechanism of Dyslipidemia in Diabetes. Insulin resistance initiates the typical triad of high triglyceride level, low HDL-cholesterol level and high small dense LDL level. When the concentration of VLDL transported triglyceride is high, CETP promotes the transfer of LDL cholesteryl ester or HDL cholesteryl ester in exchange for triglyceride. Triglyceride-rich HDL cholesterol or LDL cholesterol can undergo hydrolysis by hepatic lipase or lipoprotein lipase. Abbreviations: ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; FFA, free fatty acid; HL, hepatic lipase; LPL, lipoprotein lipase; SD LDL, small dense LDL cholesterol; TG, triglyceride. Adapted from : "Dyslipidemia in type 2 diabetes mellitus." By Mooradian AD. *Nat Clin Pract Endocrinol Metab.* 2009; 5(3):150–9.

Therefore, many international guidelines for the prevention of CVD define diabetes as a “CVD risk equivalent” and suggest similar management of cardiovascular risk factors in adults with diabetes and those with a history of CVD [9,36–38].

In prospective epidemiological studies, the incidence of many of the CVD outcomes is directly associated with the degree of hyperglycemia, as measured either by the plasma glucose or the glycated hemoglobin level (HbA1c). It had been reported that after adjustment for other risk factors, a 1% increase in the HbA1c level is associated with a 18% increase in the risk of cardiovascular events [39], and a 12–14% increase mortality risk [40,41]. This graded relationship between HbA1c, cardiovascular events and death suggested that a therapeutic strategy to lower HbA1c levels might reduce these outcomes. However, most human trials that targeted tight glucose control in T2D, in spite of preventing microvascular complications, failed to show a benefit in prevention of CVD outcomes [42–44]. A later benefit was observed if tight glucose control is initiated early in the course of disease in T1D patients [45], and in newly diagnosed T2D [46].

These findings further underline the complexity of vascular disease in diabetes and suggest that although large vessel atherosclerosis is worse in patients with diabetes, it may not be a diabetes-specific disorder [2]. It also suggests that treatment of other risk factors such as hypertension and hyperlipidemia in patients with T2D are likely as important or have a greater impact [47–50].

Management of dyslipidemia in patients with diabetes

Screening

The American Diabetes Association (ADA), recommends that fasting serum lipids should be measured at least annually in adults with diabetes, unless they present with a low-risk profile in which case lipid assessment may be done every other year [51]. Per ADA, low-risk is documented by LDL-cholesterol <100 mg/dl (2.6 mmol/L), HDL-cholesterol >50 mg/dl (1.3 mmol/L), and triglycerides <150 mg/dl (1.7 mmol/L) [51].

Treatment considerations

Lifestyle interventions

Several organizations, including the ADA and the American Heart Association (AHA), recommend that lifestyle modifications should be advocated for all patients with diabetes [51]. Such interventions include medical nutrition therapy, increased physical activity, weight loss, and smoking cessation, and each has been shown to help some patients to achieve better lipid levels. Nutrition interventions should be tailored according to patient's age, diabetes type, and other comorbidities, and should focus on avoidance of *trans* fat intake, reduction of saturated fat and cholesterol intake; increase of omega-3 fatty acids, viscous fiber (fiber such as in oats, legumes, citrus), and plant stanols/sterols [51]. Glycemic control can also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control [51].

Pharmacological interventions

There are several pharmacological classes of drugs available for treatment of dyslipidemia.

Statins

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and, thereby, suppress cholesterol biosynthesis, which results in increased LDL receptor activity and/or number. Statins are most effective in lowering LDL-cholesterol while having a modest effect on raising HDL-C and reducing TG. There are currently seven statins available in pharmaceutical form – lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin. Statins have other promising pharmacodynamic actions including: improved endothelial function, reduced vascular inflammation

and platelet aggregability, antithrombotic action, stabilization of atherosclerotic plaques, increased neovascularization of ischemic tissue, enhanced fibrinolysis and immune suppression [52].

Evidence for benefits of statin therapy in diabetes

Several clinical trials have demonstrated significant effects of statin therapy for both primary and secondary CVD prevention. Sub-analyses of diabetic subgroups of larger trials and trials specifically in subjects with diabetes showed significant primary and secondary prevention of CVD events and/or CHD deaths in diabetic patients [53–58]. Most important trial-evidence is discussed below and summarized in Table 1.

For instance, the Heart Protection Study (HPS) enrolled 5963 adults (aged 40–80 years) with diabetes who were randomly assigned to 40 mg simvastatin daily or placebo. In spite of normal total cholesterol levels at baseline, treatment with simvastatin induced a 25% significant reduction in the rates of major vascular events (major coronary event, stroke or revascularization) after 3.3 years of follow-up [54] (Table 1).

Table 1
Lipid intervention trials in diabetes.

Study	Subjects	Intervention	Main outcomes
Heart Protection Study (HPS) [54]	5963	Simvastatin 40 mg daily Placebo	25% reduction in the rates of major vascular events
Collaborative Atorvastatin Diabetes Study (CARDS) [55]	2800	Atorvastatin 10 mg daily Placebo	37% reduction in major CVD events and death
Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN) [56]	2410	Atorvastatin 10 mg daily Placebo	Composite primary end point rates were 13.7% for atorvastatin and 15.0% for placebo
Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm trial (ASCOT-LLA) [57]	2226	Atorvastatin 10 mg daily Placebo	25% reduction in the rates of major vascular events
Lescol Intervention Prevention Study (LIPS) [58]	202	Fluvastatin 80 mg daily Placebo	51% reduction in the relative risk of major cardiac events
Treating to New Targets (TNT) [59]	1501	Atorvastatin 10/80 mg daily Placebo	Rate of first major CVD event lower in atorvastatin 80 mg/day compared to 10 mg/day (13.8% vs. 17.9%)
Pavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) [60]	4162	Pravastatin 40 mg daily Atorvastatin 80 mg daily	Absolute risk reduction of 5.5% with 80 mg atorvastatin
Helsinki Heart Study (HHS) [70]	4081	Gemfibrozil 600 mg twice daily Placebo	34% reduction in incidence of CHD
Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) [71]	2531	Gemfibrozil 1200 mg daily Placebo	24% decrease in CVD events
Bezafibrate Infarction Prevention (BIP) study [73]	309	Bezafibrate 400 mg daily Placebo	7.3% reduction in the cumulative probability of fatal or nonfatal MI
Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial [77]	9795	Fenofibrate 200 mg daily Placebo	24% reduction in the risk of non-fatal MI
Acute Coronary Syndrome Israeli Surveys (ACSIS) [78]	3063	Bezafibrate + Statin Statin	30-day major adverse cardiovascular events (MACEs) was recorded in 8% patients receiving combination therapy and 14.2% of those receiving statins alone
Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial [82]	3414	Niacin 1500–2000 mg daily Placebo	16.4% first event of the composite of death from CVD in niacin group as compared to 16.2% in the placebo group

The Collaborative Atorvastatin Diabetes Study (CARDS) randomized ~2800 patients with T2D and no documented previous cardiovascular disease to either placebo or atorvastatin 10 mg/daily. The trial was terminated 2 years earlier due to a significant reduction in major CVD events and death by 37% [55], benefits evident as early as few months after starting treatment. This decrease was similar to decreases in major cardiovascular events in the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm) trial [57] and HPS [54] (Table 1).

In the ASCOT-LLA trial, in 2226 hypertensive diabetic patients without previous cardiovascular disease, atorvastatin (vs. placebo) reduced the relative risk of all cardiovascular events by 25% [57]. In the Lescol Intervention Prevention Study (LIPS), routine use of fluvastatin in patients with T2D led to a 47% reduction in the relative risk of cardiac death [58].

In contrast with these findings, the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin-dependent diabetes mellitus (ASPEN), that randomized 2410 patients with T2D to either 10 mg of atorvastatin or placebo, did not find a difference in a composite primary end point comprised of cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, coronary artery bypass surgery, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization, in spite of a significant reduction in LDL-cholesterol levels with atorvastatin [56].

In secondary CVD prevention studies, aggressive lipid lowering therapy was shown to be very effective in patients with diabetes as well. Sub studies of the Treating to New Targets (TNT) [59], and Pravastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) trials reported results for the approximately 15–25% of study participants who had diabetes [60]. Among 1501 patients with diabetes randomized in the TNT study, the incidence of the primary endpoint (time to first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related MI, resuscitated cardiac arrest, or fatal or nonfatal stroke) was significantly lower with atorvastatin 80 mg/day compared to 10 mg/day (13.8% vs. 17.9%; hazard ratio 0.75 [95%CI 0.58–0.97]; $p = 0.026$) [59]. The PROVE-IT study reported a significantly lower incidence of the primary endpoint (a composite of death from any cause, myocardial infarction, documented unstable angina requiring hospitalization, revascularization, and stroke) with intensive lipid lowering regimen compared with a standard regimen among patients with diabetes and a prior coronary event (21.1% vs. 26.6%; $p = 0.03$) [60].

A meta-analysis of 14 randomized trials of statin therapy was conducted by the Cholesterol Treatment Trialists Collaborators in 18,686 individuals with diabetes (1466 with T1D, 17,220 with T2D) and 71,370 without diabetes. During a mean follow-up of 4.3 years, there was a 9% reduction in all-cause mortality per mmol/L (38.6 mg/dL) reduction in LDL-cholesterol in participants with diabetes (rate ratio [RR] 0.91, 99% CI 0.82–1.01; $p = 0.02$), compared to 13% reduction in those without diabetes (RR = 0.87, 0.82–0.92; $p < 0.0001$). There was a significant 21% reduction in major vascular events per mmol/L reduction in LDL-cholesterol in diabetes (RR = 0.79, 99% CI 0.72–0.86; $p < 0.0001$), which was similar to the effect observed in those without diabetes (RR = 0.79, 99% CI 0.76–0.82; $p < 0.0001$). Diabetics had reductions in myocardial infarction or coronary death, coronary revascularization, and strokes. After 5 years, 42 (95% CI 30–55) fewer people with diabetes had major vascular events per 1000 allocated statin therapy [61].

Recent evidence has raised concerns of an increased risk of incident diabetes with statin use [62,63]. Some reports suggested that this risk may be limited to only those with risk factors for diabetes, and therefore such patients may benefit additionally from diabetes screening when on statin therapy [62,63]. In a collaborative meta-analysis of 13 randomized statin trials done by Sattar et al., amongst 91,140 participants on statin therapy, there was a 9% increased risk for incident diabetes (OR = 1.09, 95% CI 1.02–1.17) over 4 years. Thus, on average, treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes, while simultaneously preventing 5.4 vascular events among those 255 patients [62]. In an analysis of one of the initial studies suggesting statins are linked to risk of diabetes, the cardiovascular event rate reduction with statins outweighed the risk of incident diabetes even for patients at highest risk for diabetes [64]. The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin) [65]. The relative risk-benefit ratio favoring statins is further supported by meta-analysis of individual data of over 170,000 persons from 27 randomized trials [66]. A recent pooled analysis of data from 5 statin trials with 32,752 participants without diabetes at baseline compared intensive-dose with moderate-dose statin therapy. As compared with moderate-dose statin therapy, the number needed to harm per

year for intensive-dose statin therapy was 498 for new-onset diabetes while the number needed to treat per year for intensive-dose statin therapy was 155 to prevent cardiovascular events [67]. This demonstrated that individuals at low risk of vascular disease, including those undergoing primary prevention, received benefits from statins that included reductions in major vascular events and vascular death without increase in incidence of cancer or deaths from other causes.

There is evidence for significant LDL-cholesterol lowering from even extremely low, less than daily, statin doses [68]. When maximally tolerated doses of statins fail to significantly lower LDL-C (<30% reduction from the patient's baseline), there is no strong evidence that combination therapy should be used to achieve additional LDL-C lowering.

Very little clinical trial evidence with statins exists for T2D patients under the age of 40, or for T1D patients of any age. In the HPS subgroup <40 years and the 600 patients with T1D had proportionately similar reductions in risk as patients with T2D, although not statistically significant [54]. Similar lipid-lowering goals for both T1D and T2D patients appear reasonable, particularly if they have other cardiovascular risk factors [37].

Although adding niacin, fenofibrate, ezetimibe and bile acid sequestrants to statins would offer additional LDL-cholesterol lowering to statins alone, there is insufficient evidence that either combination therapy provides a significant increment in CVD risk reduction over statin therapy alone [37].

Current recommendations regarding statin treatment in diabetes

Based on above evidence demonstrating the higher risks for atherosclerotic vascular disease in patients with diabetes and higher case fatality rates, the ADA recommends initiation of statin therapy in all diabetic patients with overt CVD and in those without overt CVD if > 40 years of age and with one or more CVD risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria) [51]. For these individuals, using a high-dose statin to target a lower LDL-cholesterol of <70 mg/dl (1.8 mmol/l) is a suggested option.

For diabetic patients without pre-existing CVD (primary prevention) and under the age of 40, the ADA recommends to consider adding a statin if in spite of adherence to lifestyle interventions, the LDL-cholesterol remains > 100 mg/dl, and/or if they present with multiple CVD risk factors. In these individuals the current ADA guidelines recommend achieving an LDL-cholesterol goal of <100 mg/dl (2.60 mmol/L). If drug-treated diabetic patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL-cholesterol of ~30–40% from baseline is an alternative therapeutic goal [51].

The American College of Cardiology (ACC) and the AHA in collaboration with National Program to Reduce Cardiovascular Risk (NPRCR) and the National Heart, Lung, and Blood Institute (NHLBI) recently released the new 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [38]. These new guidelines emphasize prevention of heart disease and stroke, focus appropriately on statin therapy rather than alternative unproven therapeutic agents, and recognize that more intensive treatment is superior to less intensive treatment for many patients. Furthermore, the new ACC/AHA guidelines show that for individuals in whom statin therapy is clearly indicated [such as those with previous vascular disease or LDL cholesterol \geq 190 mg/dl (4.9 mmol/L)] the benefits on heart attack, stroke, and cardiovascular death significantly outweigh the risks for developing diabetes or myopathy [38].

There are underlying similarities and differences between the current ADA Cholesterol Treatment Guidelines and the revised 2013 ACC/AHA Cholesterol Treatment Guidelines. Both the ADA and the ACC/AHA recognize the high prevalence, morbidity and mortality of cardiovascular disease in patients with diabetes and the importance of primary and secondary cardiovascular disease risk reduction in this population [38,51]. Both the current ADA recommendations and the 2013 ACC/AHA Cholesterol Treatment Guidelines emphasize the importance of lifestyle (healthy diet, exercise, and weight management) in cardiovascular risk reduction and well-being, and recognize the value of high intensity statin therapy added to lifestyle therapy for patients with diabetes and overt atherosclerotic CVD, regardless of baseline lipid levels (Table 2).

Table 2

ADA and AHA/ACC positions on statins.

	ADA position [50]	AHA/ACC position [38]
Primary prevention	<ul style="list-style-type: none"> - Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients without CVD who are over the age of 40 and have one or more other CVD risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). - For lower-risk patients than the above (e.g., without overt CVD and under the age of 40), statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains above 100 mg/dL or in those with multiple CVD risk factors. - In individuals without overt CVD, the goal is LDL cholesterol <100 mg/dL (2.6 mmol/L). 	<ul style="list-style-type: none"> - Moderate-intensity statin therapy should be initiated or continued for adults 40–75 years of age with diabetes mellitus. - High-intensity statin therapy is reasonable for adults 40–75 years of age with diabetes mellitus with a $\geq 7.5\%$ estimated 10-year ASCVD risk unless contraindicated. - In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug–drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.
Secondary prevention	<ul style="list-style-type: none"> Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients with overt CVD. In individuals with overt CVD, a lower LDL cholesterol goal of <70 mg/dL (1.8 mmol/L), using a high dose of a statin, is an option. If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of ~30–40% from baseline is an alternative therapeutic goal 	<ul style="list-style-type: none"> High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤ 75 years of age who have <i>clinical ASCVD*</i>, unless contraindicated. In individuals with <i>clinical ASCVD*</i> in whom high-intensity statin therapy would otherwise be used, when either high-intensity statin therapy is contraindicated† or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. In individuals with <i>clinical ASCVD</i> >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug–drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.

Adapted from: Refs. [38,50].

There are also substantial differences. The revised 2013 ACC/AHA Cholesterol Treatment Guidelines de-emphasize lipid goal oriented treatment and use a newly developed risk prediction algorithm based on “hard” atherosclerotic events to recommend initiation of statin therapy in primary prevention patients [38]. In patients with diabetes, the threshold of greater than or equal to 7.5% is used to select between high-intensity and moderate-intensity statin regimens, defined as daily regimens that reduce LDL-cholesterol by more than 50% or between 30% and 50% [38] regardless of baseline lipid levels. As disclosed in the new guidelines, these new criteria could result in millions of additional patients being prescribed a statin, which could have unforeseen consequences. However, the evidence whether moderate-dose statins should be used for the primary prevention in all patients 40–75 years of age with diabetes, regardless of baseline lipid levels or the presence of other cardiovascular risk factors is controversial. There are also concerns that the newly proposed risk calculator [69] may be flawed as it appears to greatly overestimate risk, and thus could mistakenly suggest that millions more people are candidates for statin drugs. Moreover, patients with diabetes often have a unique pattern of dyslipidemia which may require specific consideration [51]. Additionally, there is no distinction between

patients with type 1, type 2 or other forms of diabetes or pre diabetes, where there is less high quality data (Table 2).

The increased risk for atherosclerotic cardiovascular disease and the residual excess risk of morbidity and mortality in patients with diabetes despite use of statins is an area of research of major public health importance.

Thus, based on the current levels of evidence regarding benefits and risks, high-dose intensive statin therapy appears justified for diabetic patients with preexistent CVD or in patients >40 years and at least one additional CVD risk factor. Either an LDL-cholesterol target of <70 mg/dL (1.8 mmol/L) or a reduction in LDL-cholesterol of ~30–40% from baseline, on maximal tolerated statin therapy, are reasonable goals [37,38,51].

Whether moderate-dose statins should be considered for primary prevention in all patients 40–75 years of age with diabetes, regardless of baseline lipid levels (as recommended by AHA/ACC guideline), or in patients with at least one other cardiovascular risk factor (as recommended by ADA) needs further investigation.

Therapies targeting other lipoprotein fractions

As discussed above, patients with diabetes, particularly T2D, have a unique pattern of dyslipidemia characterized by elevated triglyceride levels and low levels of HDL-cholesterol. Hypertriglyceridemia generally responds to dietary and lifestyle changes. Severe hypertriglyceridemia (>1000 mg/dl) may warrant immediate pharmacologic therapy (fibric acid derivative or fish oil) to reduce the risk of acute pancreatitis. In the absence of severe hypertriglyceridemia, targeting HDL-C or triglycerides lacks the strong evidence base of statin therapy. In diabetics with a low HDL-C and triglycerides >200 mg/dL, it is reasonable to use fenofibrate or gemfibrozil in statin intolerant diabetics.

Currently, the evidence for using specific drugs that target these lipid fractions for CVD risk reduction is significantly less robust than that for statin therapy, as discussed below.

Fibrates

The effects of fibrates on lipid metabolism are mostly mediated through the activation of peroxisome proliferator-activated receptors (PPAR-alpha). They stimulate β -oxidation of fatty acids mainly in peroxisomes (and partly in mitochondria) and therefore lower plasma levels of fatty acid and triacylglycerol. Clofibrate was the first of this class of drug discovered. Eventually, the discovery of several other fibrate drugs including ciprofibrate, bezafibrate, fenofibrate, and gemfibrozil has revolutionized lipid-lowering research. Concerns about hepatomegaly and tumor formation in the liver of rodents had restricted the widespread use of some of these drugs in humans. Currently in the U.S. only gemfibrozil and fenofibrate, due to their milder effect on peroxisome proliferation, are FDA-approved as lipid-lowering drugs.

Several large intervention trials have investigated the potential of fibrates to reduce cardiovascular events. The results have varied widely. For instance in the Helsinki Heart Study (HHS), treatment with gemfibrozil significantly reduced the primary CHD endpoint compared to placebo in a large nondiabetic population of more than 4000 participants with no evidence of CHD at baseline in [70]. In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), a secondary prevention trial that included an important diabetic subgroup, treatment with gemfibrozil induced a significant reduction in the primary CVD events endpoint compared with placebo in [71]. However, in the primary prevention World Health Organization trial treatment with clofibrate was associated with an increase in non cardiovascular mortality [72], whereas in the secondary prevention Bezafibrate Infarction Prevention (BIP) study bezafibrate failed to show an effect on the primary endpoint, although showed some benefit on reducing fatal or nonfatal MI [73]. In post hoc subgroup analyses of the HHS, VA-HIT, and BIP data, it emerged that fibrates-induced reductions in CVD events were greatest (30%–50%) in subjects with evidence of insulin resistance or other features of the metabolic syndrome, such as dyslipidemia and increased body weight [74–76]. In addition to lowering cardiovascular risk, it was suggested that fibrates may also improve insulin sensitivity in diabetic patients [71].

Studies specifically targeting patients with diabetes or metabolic syndrome provided disappointing results on hard CVD outcomes. In the subgroup analysis of the VA-HIT conducted in men with peripheral vascular disease, gemfibrozil reduced the rates of CVD events in subjects with diabetes [71]. In contrast, in the large Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial that randomized 9795 T2D subjects, fenofibrate 200 mg/daily did not result in a significant reduction in the primary composite CVD outcome after an average of 5 years follow-up compared to placebo [77]. However, there was a significant 24% reduction in the risk of non-fatal myocardial infarction and total CVD events including a 21% reduction in coronary revascularization.

Since current evidence demonstrates residual higher CVD risk in patients with diabetes despite statin treatment, it was suggested that a combination of statins with fibrates may provide additional benefit, as it would favorably target all three lipid fractions (LDL-C, triglycerides and HDL-C). However, clinical trials that specifically tested the effects of such combination did not confirm this hypothesis.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study tested the hypothesis that treatment of patients with T2D diabetes at high risk for cardiovascular disease with fenofibrate to increase plasma HDL-C levels and reduce plasma triglycerides concentrations, on the background of simvastatin therapy, would result in additional cardiovascular benefit compared with simvastatin alone. The combination did not reduce the rate of the primary outcome composed of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone [50]. Similar effects were observed in a number of secondary outcomes, including each component of the primary composite outcome tested individually, an expanded cardiovascular outcome, major coronary events, and total mortality. Prespecified subgroup analyses suggested heterogeneity in treatment effects according to sex, men having an ~16% lower primary event rate on fenofibrate, whereas women had an ~38% greater primary event rate on fenofibrate, although neither of these sex-specific effects of fenofibrate versus placebo was significant [50]. A possible benefit for patients with both triglycerides level ≥ 204 mg/dl and HDL-c level ≤ 34 mg/dl was also observed [50].

A recent analysis of 3063 patients with diabetes and acute coronary syndrome participating in the nationwide Acute Coronary Syndrome Israeli Surveys (ACSIS), evaluated the impact of combined bezafibrate and statin therapy on 30-day MACEs (a composite measure of death, recurrent myocardial infarction, recurrent ischemia, stent thrombosis, ischemic stroke, and urgent revascularization). Two-hundred and twenty-five patients (7.3%) were discharged on combined bezafibrate and statin therapy, and 2838 (92.7%) were treated with statins alone. A significantly lower risk for 30-day MACEs was observed in statin-treated patients with diabetes who also received bezafibrate, and signals regarding improvement of 30-day rehospitalization and 1-year mortality rates emerged as well [78]. However, given the retrospective nature and several other factors that could have introduced a selection bias, these findings should be cautiously interpreted.

Nicotinic acid

Epidemiologic observations have shown that in addition to elevated LDL-C levels, low levels of HDL-C are an independent predictor of CVD risk.

Niacin is the most effective currently available drug for raising HDL-C. The long term follow up of the Coronary Drug Project reported that nicotinic acid reduces CVD events [79] although the study was done in a non-diabetic cohort. Its adverse effects on glycemic control tempered the use of this agent in diabetes. More recent data showed that although niacin may increase blood glucose levels when administered in high doses, more modest doses (750–2000 mg/day) significantly improve LDL and HDL-cholesterol, and triglyceride levels, and are accompanied by only modest changes in glucose that are generally amenable to adjustment of diabetes therapy [80,81]. However, there is no evidence of a significant reduction in CVD outcomes with niacin in patients with diabetes.

Few studies assessed the efficacy of combination therapy with statins or other agents. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial tested whether extended-release niacin added to intensive statin therapy, as compared with statin therapy alone, would reduce the risk of cardiovascular events in patients with established ASCVD and atherogenic dyslipidemia (low levels of HDL-cholesterol, elevated triglyceride levels, and small, dense particles of LDL-cholesterol). Among the ~3000 patients

randomized in the AIM-HIGH trial, about one-third had diabetes. The trial was halted early due to lack of efficacy on the primary CVD outcome (first event of the composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy [82]. Hence, based on current evidence, a combination of niacin and statins cannot be recommended for CVD prevention in diabetes.

In summary

Patients with diabetes present with complex lipoprotein metabolism abnormalities. These are associated with more advanced large vessel atherosclerosis and higher CVD risk. Strong evidence demonstrates that statins are effective for both primary and secondary CVD prevention in patients with diabetes. Reduction of CVD events with statins correlates very closely with LDL-C lowering. Evidence for other classes of agents is less robust. Treatment of other risk factors such as hypertension, hyperglycemia, and obesity are also important in risk reduction in patients with diabetes.

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