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REVIEW

Atherogenic Dyslipidemia and Combination Pharmacotherapy in Diabetes: Recent Clinical Trials

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■ Abstract

Patients with type 2 diabetes (T2D) are at a markedly increased risk of cardiovascular disease (CVD). Dyslipidemia is a common risk factor and a strong predictor of CVD in T2D patients. Although statins decrease the incidence of CVD in T2D, residual cardiovascular risk remains high despite the achievement of optimal or near-optimal plasma low-density lipoprotein (LDL) cholesterol concentrations. This may, in part, be due to uncorrected atherogenic dyslipidemia. Hypertriglyceridemia, the driving force behind diabetic dyslipidemia, results from hepatic overproduction and/or delayed clearance of triglyceride-rich lipoproteins. In patients treated with a statin to LDL-cholesterol goals, the addition of ezetimibe, fenofibrate, niacin, or n-3 fatty acid ethyl esters may be required to correct the persistent atherogenic dyslipidemia. Clinical trial evidence describing best practice is limited, but recent data supports the strategy of adding fenofibrate to a statin, and suggests specific benefits in dyslipidemic patients and in the improvement of diabetic retinopathy. However, based on results from a recent clinical trial, niacin should not be added to a statin in individuals with low high-density lipoprotein cholesterol and very well controlled LDL-cholesterol. Further evidence is required to support the role of ezetimibe and n-3 fatty acids in treating residual CVD risk in statin-treated T2D patients.

Keywords: atherogenic dyslipidemia · clinical trials · pharmacotherapy · type 2 diabetes · fatty acid · lipoprotein · HDL cholesterol

1. Introduction

Dyslipidemia is a common risk factor and powerful predictor of cardiovascular disease (CVD) in high-risk patients, including those with type 2 diabetes (T2D) [1, 2]. Although low-density lipoprotein (LDL) cholesterol is the main target for treatment [3, 4], clinical trials consistently demonstrate high residual cardiovascular risk in statin-treated patients [2]. This may be because statins incompletely correct the vascular risk that is attributable to atherogenic dyslipidemia [2]. With a focus on T2D patients, we review in this article recent clinical trials employing therapeutic agents for the treatment of atherogenic dyslipidemia.

2. Atherogenic dyslipidemia

Diabetic dyslipidemia involves a cluster of lipid and lipoprotein abnormalities [5]. Elevated plasma concentrations of triglycerides and reduced high-density lipoprotein cholesterol (HDL-cholesterol), in both the fasting and postprandial states, are the core lipoprotein abnormalities [5]. The accumulation of small dense low-density lipoprotein (sdLDL) particles and triglyceride-rich lipoproteins (TRLs), including chylomicron remnants and very-low-density lipoprotein (VLDL) remnants, are also characteristic of the atherogenic lipid profile [5-8]. These abnormalities are reflected by increased plasma concentrations of non-HDL cholesterol and apolipoprotein B-100 (apoB) [6].

Abbreviations:
ACCORD - Action to Control Cardiovascular Risk in Diabetes
AHEAD - Action for Health in Diabetes
AIM-HIGH - Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes
Apo - apolipoprotein
ARBITER - Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol
CAD - coronary artery disease
CDP - Coronary Drug Project
CETP - cholesterylester transfer protein
CIMT - carotid intima-media thickness
CTT - Collaborative Treatment Trialists
CVD - cardiovascular disease
DGAT-2 - diacylglycerol acyl transferase
DHA - docosahexemoic acid
ED - endothelial dysfunction
EPA - eicosapentenoic acid
ER - extended release
FFA - free fatty acid
FIELD - Fenofibrate Intervention and Event Lowering in Diabetes
GISSI-Prevenzione - Gruppo Italian per lo Studio della Sopravvivenza nell'Infarto Miocardio GISSI-Prevenzione
HALTS - ARBITER-6-HDL and LDL Treatment Strategies in Atherosclerosis
HATS - HDL-Atherosclerosis Treatment Study
HDL - high-density lipoprotein
HPS2-THRIVE - Heart Protection Study-2 and the Treatment of HDL to reduce the incidence of vascular events
IHD - ischemic heart disease
JELIS - Japan Eicosapentenoic Acid Lipid Intervention Study
LDL - low-density lipoprotein
LpA Lipoprotein A
LPL - lipoprotein lipase
NCEP-ATP III - National Cholesterol Education Program Adult Treatment Panel III
ORIGIN - Outcome Reduction with an Initial Glargine Intervention
PLPT - phospholipid transfer protein
PPAR-α - Peroxisome proliferator-activated receptors α
PROVE IT-TIMI - Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction
REDUCE-IT - A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients with Hypertriglyceridemia and on Statin
SANDS - Stop Atherosclerosis in Native Diabetes Study
sdLDL - Small dense low-density lipoprotein
T2D - type 2 diabetes
TLC - therapeutic lifestyle change
TRL - triglyceride-rich lipoprotein
VLDL - very low-density lipoprotein

In the postprandial state, there is an increase in plasma TRLs and their remnants and qualitative changes in LDL and HDL particles [5]. Therefore, hypertriglyceridemia is a marker of a range of lipoprotein abnormalities not routinely measured in clinical practice [6]. Evidence suggests that fasting and non-fasting plasma triglyceride concentrations, and by implication triglyceride-rich apoB-containing remnant lipoproteins, are strong predictors of CVD [6-8]. Utilizing Mendelian randomization, two recent studies have demonstrated a causal association between genetically increased remnant cholesterol in hypertriglyceridemia, particularly due to genetic variation in the *apoA5* and *LPL* genes, and an increased risk of ischemic heart disease (IHD) [9, 10]. Indeed, a 1 mmol/l increase in non-fasting remnant cholesterol was associated with a 2.8-fold increase in causal risk for ischemic heart disease (IHD), independently of a reduced HDL-cholesterol [10]. The association with *apoA5* gene variants is supported by a large meta-analysis [8]. However, the evidence for a causal association between low HDL-cholesterol and atherogenesis is less compelling. Findings from a recent Mendelian randomization study challenge the concept that HDL-cholesterol raising translates to reduced risk of coronary artery disease (CAD) [11]. In the dal-OUTCOMES study, dalcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, raised HDL-cholesterol levels, but did not reduce recurrent cardiovascular events in patients with recent acute coronary syndrome [12].

3. Pathogenesis of atherogenic dyslipidemia in type 2 diabetes

Atherogenic dyslipidemia is seen in most patients with elevated triglycerides >2.2 mmol/l and reduced HDL-cholesterol <1.0 mmol/l. The majority of these patients have T2D, central adiposity, or insulin resistance [5, 6].

Etiology. The etiology of diabetic dyslipidemia is complex, and hypertriglyceridemia is central to its pathogenesis [6, 13, 14]. Diabetic dyslipidemia relates collectively to hyperglycemia [15], insulin resistance [15], hyperinsulinemia [15, 16], abdominal visceral adipose disposition, increased liver fat content [16], and dysregulated fatty acid metabolism [16]. Insulin resistance increases fatty acid flux from visceral adipose tissue to the liver, inducing hepatic steatosis, oversecretion of larger triglyceride-rich VLDL1 particles into the plasma [5, 6, 16], and a reduction in the inhibitory effect of insulin on hepatic apoB secretion [17-19]. Hyperglycemia also drives the overproduction of VLDL1, in particular increased VLDL1 triglyceride production rate [15]. Collectively, plasma glucose, insulin, and free fatty acids explain approximately half of the variation in VLDL1 production rate [15].

Impaired chylomicron clearance in T2D results from the reduced activity of lipoprotein lipase (LPL), an endothelial bound enzyme, and decreased receptor-mediated endocytosis in the liver [5, 6, 20, 21]. VLDL1 particles compete with chylomicrons and its remnants for clearance by saturating the lipolytic capacity of LPL and the activity of hepatic receptors, thereby increasing postprandial dyslipidemia [5, 6, 20]. Hepatic secretion of apolipoprotein CIII (apoCIII) is also increased in insulin resistance. This small protein, which is attached to VLDL, contributes to the delayed clearance of TRLs by inhibiting LPL and the binding of remnant TRLs to hepatic clearance receptors [6, 20]. These mechanisms collectively account for postprandial lipemia [5, 20], and may be an important causal mechanism of endothelial dysfunction (ED) in T2D; they may be treatment targets for reducing residual cardiovascular risk.

3.1 Atherogenicity

Important compositional and atherogenic changes in lipoproteins are seen in T2D [5]. An increased VLDL triglyceride pool leads to cholesterol depletion and triglyceride enrichment of LDL and HDL, mediated via the action of cholesterol ester transfer protein (CETP) [5, 6]. Increased phospholipid transfer protein (PLTP) activity may contribute to hypertriglyceridemia and compositional changes in HDL. Furthermore, the overactivity of hepatic lipase, which is commonly elevated in T2D, increases the lipolysis of triglyceride-enriched LDL and HDL particles [22, 23]. Compositional changes in HDL are also mediated by the actions of LPL [5]. Collectively, these compositional changes produce smaller and denser lipoprotein particles that are potentially more atherogenic. Small dense LDL particles more easily penetrate the arterial wall, and have a higher binding affinity to intimal proteoglycans than more buoyant larger LDL particles [5, 22, 24, 25]. In the intima, retained LDL particles are modified when exposed to oxidative stress, with sdLDL having an increased sensitivity to oxidation; glycation of LDL further increases this susceptibility to oxidation [5].

Diabetic dyslipidemia is also characterized by low HDL-cholesterol concentrations with greater reductions in HDL2 than HDL3 [5]. In parallel with these reductions in HDL particles are reductions in plasma levels of apolipoprotein A-I (apoA-I) and apoA-II and HDL lipoproteins containing both Apo A-I and Apo A-II (LpA-I:A-II) [5, 22, 26]. These compositional changes in HDL particles are important with respect to endothelial dysfunction (ED) and atherogenicity, as they are associated with the reduction in rates of reverse cholesterol transport and a decrease in the direct anti-atherogenic effects of HDL, including its antioxidant, anti-inflammatory, and anti-thrombotic effects [22, 27-29].

3.2 Targeting atherogenic dyslipidemia

Treatment for atherogenic dyslipidemia should focus on the progressing compositional changes in lipoprotein particles, aiming to reduce hepatic secretion of VLDL-apoB and -triglyceride and transfer of apoB from VLDL to LDL [6]. It should also aim to accelerate the clearance of all apoB-containing lipoproteins [6, 20]. Lifestyle changes are essential and should include low fat diets, weight loss, increased physical activity, and reduced sedentary time [6, 20]. However, pharmacotherapy is often required with statins as first line therapy [20, 30], but statins may not adequately correct the metabolic abnormalities. Therefore, combination therapies may be required [30].

4. Guideline for the management of atherogenic dyslipidemia

Several guidelines provide evidence-based recommendations for addressing diabetic dyslipidemia [3, 4, 31-35]. Two recent reports focus more specifically on elevated triglycerides and low HDL-cholesterol [36, 37]. **Table 1** summarizes the recommended treatment targets for diabetic dyslipidemia. In T2D, LDL-cholesterol lowering remains the primary focus of therapeutic interventions [3, 4, 31, 32]. T2D patients with overt CVD or high cardiovascular risk should have statin therapy and therapeutic lifestyle changes (TLCs) initiated regardless of baseline lipid levels. In lower risk patients, statin therapy should be initiated if LDL-cholesterol levels remain above 2.6 mmol/l following TLC efforts or in those with multiple CVD risk factors [31]. These recommendations are supported by evidence of CVD reduction in diabetic patients in large outcome-based clinical trials [38-41].

If LDL-cholesterol reduction is inadequate with a maximum tolerated statin dose, then adding a second therapeutic agent (ezetimibe, fibrate, or niacin) may be required [31]. For patients with elevated triglycerides (>2.3 mmol/l), the use of non-HDL cholesterol as a secondary treatment target is recommended [3, 32, 36, 37]. ApoB, a measure of LDL particle number is also a recommended treatment target in patients at cardiometabolic risk [4, 35, 37]. Recommendations for these

Table 1. Recommended treatment targets for diabetic dyslipidemia

		NCEP ATP III [3, 32]	ADA [4, 31]	NVDPA [33]	European guidelines [34-36]
LDL-cholesterol (mmol/l)	Very high risk	<1.8	<1.8	<2.0	<1.8
	High risk	<2.6	<2.6	<2.0	<2.5
Triglycerides (mmol/l)			<1.7	<2.0	<1.7
HDL-cholesterol (mmol/l)	Male		>1.0	≥1.0	>1.0
	Female		>1.3	≥1.0	>1.2
Non-HDL cholesterol (mmol/l)	Very high risk	<2.6	<2.6	<2.5	<2.6
	High risk	<3.4	<3.4	<2.5	<3.3
ApoB (g/l) [3, 7]	Very high risk		<0.8		<0.8
	High risk		<0.9		<1.0

Legend: NCEP ATP III - Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); ADA - American Diabetes Association; NVDPA - National Vascular Disease Prevention Alliance of Australia.

patients include combination therapy with a second lipid-regulating agent (fibrate, niacin, or omega-3 fatty acids) or intensification of LDL-cholesterol lowering [3, 4, 36]. Evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study supports the use of combined statin and fenofibrate therapy in hypertriglyceridemic T2D patients [42].

5. Therapeutic regulation of atherogenic dyslipidemia in type 2 diabetes

5.1 Monotherapies

Lifestyle interventions. Initial management should include a personalized lifestyle modification program to optimize weight loss, lipids, and glycemic control. Evidence suggests that lifestyle programs aimed at achieving weight loss improve many of the metabolic abnormalities in T2D that are associated with ED and CVD, such as hyperglycemia, insulin resistance, visceral obesity, hypertension, and dyslipidemia. Weight loss improves the lipoprotein dysregulation in obese subjects with metabolic syndrome and T2D [20, 43-45]. Benefits of weight reduction in T2D increase steadily with increasing weight loss and include reductions in waist circumference, blood pressure, fasting glucose, HbA1c, and serum triglycerides, resulting in improved metabolic control and CVD risk factor reduction [46, 47].

In the Look AHEAD (Action for Health in Diabetes) study, weight loss and improved physical fitness in type 2 diabetic patients was associated with improved glycemic control and CVD risk factor reduction [47, 48]. After 4 years of follow-up in the Look AHEAD study, intensive lifestyle intervention was associated with greater weight loss and improvements in physical fitness [48]. Improvements in glycemic control, blood pressure, triglycerides, and HDL-cholesterol were also demonstrated [48]. In T2D patients, a reduction in insulin resistance and fat mass following prolonged aerobic exercise resulted in an improved lipoprotein metabolism [49].

Should dyslipidemia persist following a trial of intensified lifestyle changes, the next approach is pharmacotherapy, either an intensification of statin therapy or the addition of a second lipid regulating agent.

Lipid regulating therapy. (*i*) Statin monotherapy: Patients with an increasing number of metabolic syndrome components, with or without diabetes, have a progressive risk of CVD, and derive greater incremental benefit from higher dose statin therapy [50]. Statins, the most potent agents for lowering plasma LDL-cholesterol and apoB concentrations, have a less potent but significant effect on reducing plasma triglycerides [6]. Indeed, statin therapy in hypertriglyceridemic patients, with and without T2D, has been shown to reduce triglyceride concentrations by up to 45% [51-55], in a dose-dependent manner and proportional to LDL-cholesterol lowering [54, 55]. Statin-treated patients with combined low LDL-cholesterol (<1.8 mmol/l) and low triglyceride (<1.7 mmol/l) levels had the lowest coronary heart disease (CHD) event rate in the PROVE IT-TIMI 22 trial [56]. Evidence suggests that statins may mediate triglyceride-lowering in T2D by increasing the catabolism of

TRL- triglyceride [52] and TRL's VLDL1-ApoB, VLDL2-ApoB, and IDL-ApoB [57]. The more potent statin, rosuvastatin, has been shown to further mediate triglyceride lowering by reducing the production rate and secretion of VLDL1-ApoB [57]. However, this effect has not consistently been shown with statin therapy, indicating that limiting *de novo* cholesterol synthesis is insufficient for reducing the effects of insulin resistance on hepatic VLDL production [6, 20, 58, 59]. Hence, targeting the hepatic production of triglycerides by additional measures such as lifestyle or other pharmacotherapy is required to optimize the management of dyslipidemia in T2D.

However, several large clinical trials have shown that statins decrease cardiovascular events in T2D patients, attaining an average 20% reduction in CVD events per 1 mmol/l decrease in LDL-cholesterol [41]. In coronary patients with T2D or with the metabolic syndrome alone, high-dose statin (atorvastatin 80 mg daily) decreased the relative risk of CVD by 25-30% compared with lower-dose statin (atorvastatin 10 mg daily) [60]. Evidence also supports the use of statins in T2D patients without CVD, but with at least one other cardiovascular risk factor, including hypertension [39, 61]. These findings are consistent with the Heart Protection Study (HPS) [38] and the Collaborative Treatment Trialists' (CTT) Collaborators meta-analysis of statin trials in 18,686 people with diabetes [41]. The cardiovascular benefits of statins relate primarily to the lowering of LDL-cholesterol and lipoprotein remnants, but residual cardiovascular risk in statin-treated patients remains high [2, 41]. In T2D, residual cardiovascular risk extends to both macroangiopathy and microangiopathy [2].

(*ii*) Fibric acid derivatives: A meta-analysis has concluded that fibrates are effective in reducing CVD events, primarily by prevention of coronary events [62]. Another recent meta-analysis also suggested that fibrates may be particularly useful in improving dyslipidemia and preventing CVD in people with mild to moderate chronic kidney disease, including diabetics [63]. The lipid-regulating effects of fibrates, mediated via the peroxisome proliferator-activated alpha (PPAR-α) receptor, predominantly promote fatty acid catabolism and reverse cholesterol transport, resulting in triglyceride lowering and increased HDL-cholesterol and LDL particle size [64]. Fibrates can lower plasma triglyceride and LDL-cholesterol concentrations by up to 50% and 20%, respectively. Fibrates also increase HDL-cholesterol by up to 20%, and enhance the formation of large, less dense LDL-particles [42]. Clinical trials also confirm the benefits of fibrates in T2D patients [42, 65-67]. In a subgroup analysis of the Helsinki Heart Study, diabetic patients, when compared with non-diabetic subjects, were more dyslipidemic, at higher CVD risk, and achieved a modest but non-significant reduction in CVD risk with gemfibrozil therapy [65]. Although the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study did not select T2D patients for having atherogenic dyslipidemia, a *post-hoc* analysis of patients with triglycerides ≥2.3 mmol/l demonstrated that fenofibrate reduced CVD events in hypertriglyceridemic T2D patients with or without low HDL-cholesterol [67]. The greatest benefit was seen in those patients with triglycerides ≥2.3 mmol/l and reduced HDL-cholesterol (<1.0 mmol/l); a relative risk reduction of 27% was demonstrated [67]. In FIELD, improvement in microangiopathy was also demonstrated, reflected by reductions in albuminuria [68], laser photocoagulation [69], and minor amputations [70]. However, the aforementioned evidence is confined to T2D patients not taking background statin therapy. Evidence for the effects of combination statin plus fibrate therapy on CVD outcomes is currently limited to the ACCORD study. ACCORD recently reported on the efficacious effect of adding fenofibrate to ongoing simvastatin therapy on CVD events in T2D patients [42]. ACCORD will be discussed in a subsequent section.

(*iii*) Nicotinic acid (niacin): At therapeutic doses, niacin exerts a global improvement in lipid and lipoprotein metabolism, and remains the most efficacious therapy available for increasing HDL-cholesterol [30, 71, 72]. Niacin has been shown to decrease plasma triglycerides and LDL-cholesterol by up to 35% and 15%, respectively, and increase HDL-cholesterol by up to 30% in a dose dependent manner [30]. Many of niacin's effects are thought to derive from its action on adipose tissue [73]. However, the cellular mechanism for niacin's lipid-lowering effects were not fully elucidated until the identification of a G protein-coupled receptor GPR109A (HM74A) in 2003, which is highly expressed in adipose tissue, acts as a high-affinity receptor for nicotinic acid, and mediates antilipolytic effects [72, 74-77]. By binding to GPR109A, niacin inhibits hormone-sensitive lipase activity, resulting in decreased free fatty acid (FFA) release from adipose tissues. This results in a decreased flux of FFA to the liver that may reduce triglyceride production and subsequent hepatic VLDL production [45, 74, 78]. Niacin may also directly and noncompetitively inhibit hepatic

diacylglycerol acyl transferase (DGAT-2), the key enzyme in triglyceride synthesis [45, 79]. A mechanism for niacin's HDL raising effect remains to be fully elucidated, but it may involve the down-regulation of the HDL-catabolism receptor, resulting in delayed catabolism of larger HDL particles [71, 78, 80, 81]. Furthermore, kinetic studies suggest that niacin may increase the secretion of HDL-apoA-1 [82]. The lipid-regulating effects of niacin may be further mediated through PPAR-mediated transcriptional regulation, and may involve all three PPAR isoforms, alpha (α), gamma (γ) and delta (δ) [73].

It was suggested in the Coronary Drug Project (CDP) that niacin monotherapy may decrease cardiovascular events and mortality [6, 30, 83, 84], with post-trial follow-up demonstrating that the benefits were independent of hyperglycemia, metabolic syndrome, and diabetes [6, 30, 85, 86]. This is important as it has been suggested that niacin impairs glucose/insulin homeostasis [87]. Niacin significantly improves diabetic dyslipidemia [88], and any deleterious effects on glycemic control can be offset by adjusting antidiabetic therapy [89]. The effects of niacin on background statin therapy is discussed in a subsequent section.

(*iv*) N-3 fatty acid ethyl esters: Supplementation with n-3 fatty acid ethyl esters (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), dose dependently lowers plasma triglycerides, particularly in patients with hypertrigylceridemia [6, 20]. Doses of 3-4 g daily of EPA and DHA are required. Therefore, commercially available concentrates of n-3 fatty acid ethyl esters, such as omacor, are required for lowering plasma triglycerides [6]. These are FDA approved, as an adjunct to diet, to mitigate the risk of pancreatitis in patients with plasma triglycerides >5.5 mmol/l [6]. Improved triglyceride metabolism by n-3 fatty acids involves several mechanisms, including the transcriptional regulation of hepatic genes involved in lipogenesis and fatty acid oxidation [6, 90]. N-3 fatty acids decrease the hepatic secretion of large-size VLDL in patients with the metabolic syndrome and T2D, explaining the fall in triglycerides in those receiving a statin [6, 20, 91]. There is an increased conversion of VLDL to LDL, but the elevation of LDL-cholesterol can be counteracted by a statin [6, 20].

In the Gruppo Italian per lo Studio della Sopravvivenza nell'Infarto Miocardio GISSI-Prevenzione (GISSI-Prevenzione) study, combination EPA/DHA dosed at 1 g daily reduced all-cause mortality and sudden death in subjects with previous myocardial infarction [92]. N-3 fatty acid supplementation in the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial is discussed in a subsequent section [93]. A comprehensive review of the cardiovascular effects of omega-3 fatty acids has recently been published [94].

5.2 Addressing residual cardiovascular risk with combination pharmacotherapy: recent clinical trials

High residual cardiovascular risk is evident in statin-treated T2D patients [39, 41]. This residual risk may relate to persistent abnormalities in TRLs and HDLs which are not fully corrected by statins [56, 95]. Increasing statins may partially improve these lipoprotein abnormalities, but increases the risk of musculoskeletal side effects [96], to which diabetic patients are prone [6]. Evidence for the addition of ezetimibe, fibrates, niacin, and n-3 fatty acid ethyl esters as adjunctive treatments for residual dyslipidemia and CVD risk are discussed below.

Statins and ezetimibe. Ezetimibe, an intestinal cholesterol absorption inhibitor, lowers LDL-cholesterol by 10 to 20%. However, its effects on triglycerides and HDL-cholesterol are minor [6, 97]. It does this chiefly by increasing the catabolism of LDL and possibly IDL-apoB-100 by upregulation of hepatic receptors. This relates to the impact of inhibiting intestinal cholesterol absorption on hepatic cholesterol content [6, 20]. Combination statin/ezetimibe therapy has complementary effects on the catabolism of apoB-containing lipoproteins through "dual inhibition" of cholesterol synthesis and absorption [6, 20]. In T2D patients, combination ezetimibe with lower-dose statin therapy achieved LDL-cholesterol and non-HDL-cholesterol targets more effectively than statin alone [98]. In the Stop Atherosclerosis in Native Diabetes Study (SANDS), lowering of LDL-cholesterol to aggressive targets with ezetimibe plus statin, or statin alone, achieved regression of carotid intima-media thickness (CIMT), a surrogate marker of atherosclerosis, in T2D patients [99]. This related to the reduction in LDL-cholesterol and not the minimal changes in triglycerides or HDL-cholesterol [99]. Hence, further evidence is required to support the role of ezetimibe in treating residual CVD risk in statin-treated T2D patients.

Statins and fibrates. A recent pooled analysis of two controlled studies reported on the benefits of

rosuvastatin and fenofibrate, alone or in combination, in patients with mixed dyslipidemia [100]. Patients were stratified according to high, moderate, and low CVD risk based on National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines. Rosuvastatin alone or in combination had similar effects on patients achieving LDL-cholesterol goals. However, combination therapy had a more favorable effect on total atherogenic burden compared with fenofibrate alone; a greater percentage of moderate- and high-risk patients achieve non-HDL target levels and ApoB <0.9 g/l in the high risk group [100].

A limited number of controlled studies have reported on the effects of combination statin plus fibrate therapy on CVD outcomes. The benefits of combined fibrate and statin therapy was examined in the ACCORD study.

(*i*) Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid study: ACCORD-Lipid reported on the effects of adding fenofibrate to ongoing statin treatment in 5518 T2D patients who had documented CVD or a least two additional cardiovascular risk factors, on a background of good glycemic and blood pressure control [42]. Patients already at LDL-cholesterol target (~2.6 mmol/l on a mean dose of 22 mg/day of simvastatin) were randomized to fenofibrate (54-145 mg/day) plus simvastatin (20-40 mg/day) or simvastatin (20-40 mg/day) alone. However, as the ACCORD trial also targeted glycemic control, the lipid arm was not restricted to patients with atherogenic dyslipidemia. Compared to simvastatin alone, 4.7 years of combination therapy did not reduce the rate of major fatal or nonfatal cardiovascular events. Compared with simvastatin alone, fenofibrate significantly reduced plasma triglycerides (-22% vs. -8.7%) and, although modest, a significant increase in HDL-cholesterol (+8.4% vs. +6.0%) was demonstrated. No significant differences were reported in LDL-cholesterol, which averaged 2.0 mmol/l in both groups. Fenofibrate significantly reduced the incidence of both microalbuminuria and macroalbuminuria. However, in a valid pre-specified analysis of patients with triglycerides >2.3 mmol/l and HDL-cholesterol <0.9 mmol/l (approximately 17% of the ACCORD-Lipid population), combined therapy achieved an additional 31% reduction in cardiovascular risk, though this did not achieve statistical significance. ACCORD Lipid did not support the use of combined statin and fenofibrate therapy in the majority of T2D patients, but in those who had hypertriglyceridemia with or without low HDL-cholesterol, adding a fibrate was beneficial in reducing residual CVD risk, despite intensification of statin therapy.

(*ii*) ACCORD-Eye trial: In a subgroup of 2856 T2D patients, ACCORD-Eye investigated the effects of intensive glycemic control (glycated hemoglobin <6% vs. 7.0 to 7.9%), systolic blood pressure (<120 vs. <140 mmHg) and combination therapy for dyslipidemia (fenofibrate plus simvastatin vs. simvastatin alone) on retinopathy, assessed using fundal photography [101]. At 4 years, progression of retinopathy reduced significantly with improved control of glycemia (10.4% vs. 7.3%, p = 0.003), and dyslipidemia (10.2% vs. 6.5%, p = 0.006), but not with blood pressure control (8.8% vs. 10.4%, p = 0.29). Neither improved control of glycemia nor dyslipidemia had a significant effect on moderate vision loss. Progression of retinopathy with fenofibrate was apparently global and not confined to patients with diabetic dyslipidemia. The microvascular benefits of intensive glycemic control were counteracted by an increase in total and cardiovascular disease-related mortality, weight gain, and hypoglycemia [102]. That intensive blood pressure control did not reduce retinopathy progression may reflect the narrow range of blood pressure, small treatment effect, and short duration of the intervention [6, 101].

(*iii*) Implications of ACCORD: ACCORD-lipid supports recommendations that fibrates, in particular fenofibrate, may be used to treat residual dyslipidemia in statin-treated T2D patients [3, 4, 34]. Because ACCORD tended to recruit patients with low HDL-cholesterol, a conservative estimate of the proportion of T2D patients requiring the addition of fenofibrate is more likely to be ≤10%, especially in those treated with more potent statins [6]. Dyslipidemia is a risk factor for retinopathy [103], and, in the presence of both, the addition of fenofibrate to a statin may have value [6].

Statins and niacins. Combination therapy with a statin and niacin is associated with regression of coronary atherosclerosis and carotid intima-media thickness (CIMT) in patients at high cardiovascular risk with low HDL-cholesterol levels, including those with diabetes [104-107]. In the HDL-Atherosclerosis Treatment Study (HATS), combined statin and niacin therapy slowed the progression of coronary atherosclerosis in patients at high cardiovascular risk with low HDL-cholesterol levels, including those with diabetes [104]. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) study, reported a significant inhibition in the progression of ultrasonographic CIMT in patients with known CAD and low levels of HDL-

cholesterol, of whom 50% had the metabolic syndrome and 28% diabetes following 12 months of combination simvastatin and extended release (ER) niacin (Niaspan®) [105]. Patients who completed ARBITER 2 were subsequently enrolled in a follow-up study (ARBITER 3) [106]. In this follow-up study, a significant additional regression in CIMT was demonstrated over 24 months of treatment with ER niacin. ER niacin was also associated with a 23% increase in HDL-cholesterol, and this increase was independently associated with CIMT regression [106]. The ARBITER-6-HDL and LDL Treatment Strategies in Atherosclerosis (HALTS) study enrolled patients with CVD or CVD risk equivalent who were treated with long-term statin therapy to LDL-cholesterol levels <2.6 mmol/l, but who had residual low HDL-cholesterol levels. Patients were randomized to receive either ER niacin or ezetimibe [107]. The addition of ER niacin achieved a significant regression in CIMT compared with progression in CIMT with ezetimibe, despite a greater reduction in LDL-cholesterol with ezetimibe [107]. These beneficial effects may reflect the reduction in triglycerides and increase in HDL-cholesterol seen with ER niacin [6].

However, given the recent negative reports from the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL-cholesterol/High Triglyceride and Impact on Global Health Outcomes) study and the HPS2-THRIVE (Heart Protection Study-2 and the Treatment of HDL to reduce the incidence of vascular events), caution is indicated with the addition of niacin to statins in individuals with low HDL-cholesterol. AIM-HIGH was discontinued after 36 months of follow-up due to lack of clinical benefit from the addition of ER niacin to statin (± ezetimibe) therapy, despite significant improvements in HDL-cholesterol and triglycerides [108]. A further consideration in discontinuing AIM-HIGH was an increased stroke risk, but overall this was less than 1% and previous studies have not demonstrated an increased stroke risk with niacin.

A recent report from the AIM-HIGH trial suggests a non-significant trend towards benefits with the addition of ER niacin in a subset of patients in both the highest triglyceride and lowest HDL-cholesterol tertiles ($p = 0.073$) [109]. However, the investigators concluded that lipoprotein levels were not predictive of the differential benefit or harm with niacin treatment [109]. HPS2-THRIVE compared tredaptive (ER niacin 2 g plus laropiprant (an antiflushing agent) 40 mg daily) with placebo in 25, 673 patients treated with simvastatin plus ezetimibe if required. Following 3.9 years of follow-up, no significant benefit was demonstrated on the primary endpoint of major cardiovascular events, and a four-fold greater rate of myopathy was reported with tredaptive across all subgroups [110, 111]. Importantly, the safety data showed an excess of new onset diabetes, diabetic complications, infections, bleeding (gastrointestinal (GI) and intracranial), and GI symptoms with tredaptive. A caveat is that the volunteers were mainly Chinese and had very well-controlled LDL-cholesterol (1.6 mmol/l at baseline), so that the use of this agent, which has now been withdrawn from the market by Merck, should not be used in people with low HDL cholesterol/high triglyceride and LDL-cholesterol at target. A recent review suggests that the CV benefits of niacin alone may be independent of effects on HDL-cholesterol [112]. Whether any such benefits from niacin ER in HPS2-THRIVE were nullified by laropiprant, a prostaglandin D2 inhibitor, remains open to question.

Statins and n-3 fatty acids ethyl esters. Evidence suggests combined statin and n-3 fatty acids may reduce cardiovascular events in both a primary and secondary prevention setting. The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS) demonstrated a reduction in major cardiovascular events with combined n-3 fatty acids (EPA 1800 mg daily) and low-dose statin (pravastatin 10 mg or simvastatin 5 mg daily) compared with statin alone [113]. However, this cardiovascular benefit may relate in part to the antiarrhythmic effects of n-3 fatty acids, and is independent of minor changes in plasma triglycerides [6, 20]. The ORIGIN trial found a lack of cardiovascular benefit with daily supplementation of 1 g of n-3 fatty acids (omacor) in patients with or at risk of T2D (50% treated with a statin) [93]. The benefit of adding higher-dose EPA to statins in hypertriglyceridemic subjects at high CVD risk is currently being tested in the REDUCE-IT trial (A Study of AMR101 to Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients with Hypertriglyceridemia and on Statin) [114].

6. Conclusions

Type 2 diabetic patients are at a markedly increased risk of CVD events. Dyslipidemia is a common risk factor and a strong predictor of CVD in T2D patients. Although statins decrease the in-

cidence of CVD in T2D, residual cardiovascular risk remains high, despite the achievement of optimal or near-optimal plasma LDL cholesterol concentrations. This may, in part, be due to uncorrected atherogenic dyslipidemia. Therapeutic interventions, including lifestyle changes and lipid-regulating agents, correct diabetic dyslipidemia via several mechanisms. Recent evidence suggests that residual diabetic dyslipidemia and cardiovascular risk in statin-treated patients with T2D may be targeted with fenofibrate. At present, there are no clinical end-point trials supporting the addition of ezetimibe or marine-derived n-3 polyunsaturated fatty acids. In our opinion and on the basis of a recent clinical trial, niacin should not be added to a statin in individuals with low high-density lipoprotein cholesterol and very well controlled LDL-cholesterol.

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