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Treatment of Dyslipidemias to Prevent Cardiovascular Disease in Patients with Type 2 Diabetes

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Abstract

Purpose of Review—Current preventive and treatment guidelines for type 2 diabetes have failed to decrease the incidence of comorbidities, such as dyslipidemia and ultimately heart disease. The goal of this review is to describe the physiological and metabolic lipid alterations that develop in patients with type 2 diabetes mellitus. Questions addressed include the differences in lipid and lipoprotein metabolism that characterize the dyslipidemia of insulin resistance and type 2 diabetes mellitus. We also examine the relevance of the new AHA/ADA treatment guidelines to dyslipidemic individuals.

Recent Findings—In this review, we provide an update on the pathophysiology of diabetic dyslipidemia, including the role of several apolipoproteins such as apoC-III. We also point to new studies and new agents for the treatment of individuals with type 2 diabetes mellitus who need lipid therapies.

Summary—Type 2 diabetes mellitus causes cardiovascular disease via several pathways, including dyslipidemia characterized by increased plasma levels of apoB-lipoproteins and triglycerides, and low plasma concentrations of HDL cholesterol. Treatments to normalize the dyslipidemia and reduce the risk for cardiovascular events include the following: lifestyle and medication, particularly statins, and if necessary, ezetimibe, to significantly lower LDL cholesterol. Other treatments, more focused on triglycerides and HDL cholesterol, are less well supported by randomized clinical trials and should be used on an individual basis. Newer agents, particularly the PCSK9 inhibitors, show a great promise for even greater lowering of LDL cholesterol, but we await the results of ongoing clinical trials.

Keywords

Diabetes; Lipids; Lipoproteins; Dyslipidemia; Treatments; Cardiovascular disease

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Compliance with Ethical Standards

Conflict of Interest Maryam Khavandi has no conflicts related to this article.
Gissette Reyes-Soffer consults for Merck, Inc. and Genzyme, Inc. and has given lectures for Sanofi/Regeron and Merck.
Henry Ginsberg consults for or has given lectures for Sanofi-Regeneron, Merck, Amgen, Kowa, Ionis, AstraZeneca, Bristol-Myers Squibb, Resverlogix, Lilly, and Pfizer.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Despite current treatment guidelines and prevention campaigns, the incidence and prevalence of type 2 diabetes mellitus (T2DM) doubled between 1980 and 2012 with further rises noted in minorities such as Hispanics and African Americans [1]. In the USA in 2014, the number of newly diagnosed cases of T2DM was approximately 1.4 million [2].

Atherosclerotic cardiovascular disease (ASCVD) is the number one cause of death globally and accounts for 37% (out of 16 million deaths) of the deaths due to noncommunicable diseases in those individuals under the age of 70 [3]. ASCVD is the major cause of morbidity and mortality in people with T2DM [4]; therefore, reducing ASCVD should be a top priority to reduce mortality and morbidity, improve quality of life, and lessen lifestyle and economic burdens in individuals with T2DM. Although numerous processes contribute to ASCVD in diabetes mellitus, this review will mainly focus on the pathophysiology of dyslipidemia in T2DM, guidelines for the reduction of ASCVD in people with T2DM, and current treatments to achieve the goals of those guidelines.

Lipoprotein Metabolism and Type 2 Diabetes Mellitus

Understanding normal lipid and lipoprotein metabolism is crucial for the development of treatment guidelines and pharmaceutical agents that target the dyslipidemia of T2DM. Lipoproteins are macromolecular complexes consisting of core lipids [mainly triglycerides (TG) and cholesteryl esters (CEs)], surface phospholipids, free cholesterol, and one or more apolipoproteins. There are five distinct major classes of lipoproteins: chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL may be referred to as VLDL remnants), low-density lipoproteins (LDL), and high-density lipoproteins (HDL); these have been defined based on physical characteristics, molecular weight, diameter, and chemical composition. In addition, surface apolipoproteins provide structural stability and are important in defining the functions of each class of lipoprotein particles [5, 6]. Although a detailed description of lipoprotein metabolism is beyond the scope of this manuscript, a brief overview, together with the abnormalities present in T2DM, is in order (more detailed reviews of lipid metabolism have been recently published [7, 8]).

In the postprandial state, TG and CE derived from the diet are carried into and through the circulation on intestinally derived chylomicrons. These very large and buoyant lipoproteins are assembled in enterocytes in response to absorption of TG and cholesterol and require apolipoprotein B48 (apoB48), which is a truncated form of apoB100. Active microsomal triglyceride transfer protein (MTP) to package apoB48 with the neutral core lipids, TG and CE. The role of chylomicron is to deliver dietary energy, in the form of TG-derived fatty acids (FA) to adipose tissue and muscles, a process that is mediated by lipoprotein lipase (LpL). Lipolysis is modulated by apoCII, a required activator, and apoCIII, an inhibitor of LpL-mediated lipolysis. Other players in this process are apoA5, which can stimulate LpL, and the angiopoietin-like proteins (angptl3 and angptl4), which can interfere with LpL activity. After majority of TG is delivered to the adipose tissue and muscle via lipolysis, the chylomicron remnants that are generated acquire apolipoprotein E (apoE) from HDL particles. Through the actions of cholesteryl ester transfer protein (CETP), remnants are also enriched in CEs derived from exchange of core lipids with LDL and HDL. Ultimately,

chylomicron remnant particles are cleared by the liver through the interactions of apoE with the hepatic LDL receptors, the LDL receptor-related protein (LRP), and/or cell-surface heparan sulfate proteoglycans. ApoCII and CIII can each modulate chylomicron clearance into the liver by interfering with the binding of apoE to its receptors [6, 9, 10, 11, 12, 13]. Further lipolysis of chylomicron remnant TG by hepatic lipase (HL) may augment uptake of the particles by the liver.

In T2DM, which has insulin resistance (IR) as a core abnormality, postprandial lipid and lipoprotein metabolism are altered. Studies in diabetic animal models have demonstrated increased intestinal secretion of apoB48-containing lipoproteins, accompanied by increased expression, mass, and activity of intestinal (MTP) [14] [15, 16, 17]. Similar findings have been reported in humans with IR/T2DM and seems to be driven both by increased FA levels in the plasma that are taken up by enterocytes and the insulin-resistant state itself [18, 19]. Thus, there are more possibly smaller chylomicrons entering the circulation after consumption of a fatty meal by individuals with T2DM, raising the possibility of competition amongst chylomicron (and VLDL) for LpL [20]. The chance for decreased efficiency of LpL-mediated lipolysis due to increased numbers of chylomicron T2DM is exacerbated by modestly decreased LpL activity in IR states and an increase in apoCIII relative to apoCII levels. Increased apoCIII secretion into the plasma has been demonstrated in patients with diabetes and hypertriglyceridemia [21, 22], and this may also reduce hepatic uptake of chylomicron remnants. There have also been reports of alterations in hepatic heparin sulfate proteoglycans in mouse models of diabetes, potentially further negatively affecting remnant removal by the liver.

Throughout the day, during both fasting and postprandial states, the liver assembles and secretes VLDL. The driving force for VLDL secretion is mainly the maintenance of normal hepatic TG levels, although hepatic cholesterol metabolism also can affect VLDL production. Three major sources of hepatic TG-FAs can be involved in VLDL assembly: circulating FAs derived from adipose tissue and taken up by the liver, FAs derived from chylomicron and VLDL remnants uptake by the liver, and FAs produced from glucose by hepatic de novo lipogenesis (DNL). Of these three, circulating FAs are by far the major source of TG-FAs in the liver [23]. IR, with or without T2DM, increases hepatic FA flux to the liver from the adipose tissue by reducing insulin’s antilipolytic effects on adipocytes. The importance of FA uptake by the liver for VLDL secretion has been demonstrated in mice infused with oleic acid bound to albumin [22] and in both mice and humans receiving lipid emulsions and heparin [24, 25]. Uptake of TG-containing chylomicrons and VLDL can also stimulate assembly and secretion of VLDL [26, 27]. Finally, in animal models, increased hepatic DNL stimulates VLDL-TG secretion but, unlike increased uptake of FA or remnants from the circulation, which stimulates secretion of both apoB and TG, increases in DNL are associated with secretion of the same number of larger, more TG-rich particles [28, 29]. These findings are consistent with increased rates of DNL in people with T2DM [30] and increased secretion of the more buoyant and TG-rich VLDL1 subclass in the same group [31]. In fact, the major factors correlating with secretion of VLDL1 are hepatic fat and glycemia [32, 33]. Importantly, however, IR/T2DM is also associated with assembly and secretion of VLDL particles as measured by the secretion rates of apoB100 [31].

The major role of VLDL is to deliver energy from the liver to the peripheral tissues. It is not surprising, therefore, that the metabolism of VLDL particles initially parallels that of chylomicrons (apoB48-containing lipoproteins). Hydrolysis of VLDL TG by LpL is key for the delivery of VLDL TG-FA to the adipose tissue and muscle, and this process can be modulated by all the factors that affect chylomicron lipolysis: apoCII, apoCIII, apoA5, and the angptl proteins [34, 35]. Lipolysis yields smaller, denser VLDL remnants, IDL, and chylomicrons; the efficiency of lipolysis is, however, impaired in type 2 DM. Hepatic uptake of VLDL remnants and chylomicron share similar pathways and these are also affected in insulin-resistant states. HL can further catabolize VLDL-remnant TG, yielding LDL [36].

LDL comprises a heterogenous family of several subclasses defined by differences in their density, size, chemical composition, and electrical charge [37, 38]. The basis of this heterogeneity is not completely understood, although hypertriglyceridemia and prolonged residence time in the plasma of VLDL and IDL appear to lead to a broader spectrum of LDL particles. CETP-mediated exchange of LDL CE for VLDL or chylomicron TG, resulting in a TG-enriched and CE-depleted LDL particle that can then undergo lipolysis by LpL or HL, produces the small, dense, and CE-poor LDL (sdLDL). Thus, in the dyslipidemia of T2DM, there is an increase in sdLDL, which has been the focus of many epidemiologic studies indicating its increased association with cardiovascular disease (CVD) risk [39]. However, since sdLDL is associated with all the other abnormalities of the diabetic dyslipidemia, as well as the CVD risk factors of IR, including hypertension and obesity, any specific atherogenic characteristic of sdLDL can be questioned. It is important to note, however, that for any level of circulating LDL cholesterol, there are more LDL particles (and a higher apoB concentration) in people with the dyslipidemia of IR/T2DM than in normal subjects, and all apoB particles are atherogenic [40].

The HDL class is considerably different in structure and function from apoB-containing lipoproteins. The formation of HDL begins with the ATP-binding cassette transporter A1 (ABCA1) transferring intracellular and plasma membrane free (unesterified) cholesterol to phospholipid disks with apolipoprotein AI on its surface. This first step in the generation of mature HDL occurs in both the liver and the intestine, which is the source of about 75% of circulating HDL [40]. The maturation of HDL results from the conversion of free cholesterol to CE by the enzyme lecithin:cholesterol acyltransferase (LCAT), which is activated by apoA-I. CEs move from the surface to the core of the maturing HDL particle, allowing addition of more free cholesterol to the surface, followed by more CE generation. As HDL matures, additional free cholesterol can also be added via ATP-binding cassette transporter G1 (ABCG1) and scavenger receptor B1 (SRB1), giving rise to mature, CE-rich HDL. Mature HDL particles can deliver both free and esterified cholesterol to the liver via interaction with SRB1 [41, 42]. This process has been called reverse cholesterol transport (RCT); it has yet to be proven, however, that RCT is critical for “clearing” cholesterol from peripheral tissues, including foam cells in arterial plaques to the liver [42, 43]. Attempts to alter RCT have, to date, failed in humans.

In the presence of T2DM, multiple factors acting in concert result to lower levels of HDL-C and apoAI. CETP-mediated exchange of TG for CE in both the fasting and postprandial states clearly plays an important role. TG enrichment of HDL is followed by lipolysis of TG

leading to generation of smaller HDL particles from which apoA-I can dissociate [44, 45•]. The free apoA-I can be filtered through the glomerulus and then taken up and degraded by renal tubular cells [44]; this increased clearance of apoA-I from the plasma, confirmed by HDL turnover studies demonstrating increased apoA-I fractional removal rates, is the hallmark of low levels of the protein and HDL-C in states of IR and low HDL [44, 46]. Thus, CETP-mediated mechanisms result to less CE in HDL and fewer HDL particles. However, IR itself lowers HDL levels by pathways that are not fully understood. Recent studies demonstrated that when hepatic insulin signaling is reduced, apoA-I gene expression and protein synthesis is decreased by a mechanism involving type 1 deiodinase in the liver [47]. Increased hydrolysis of HDL phospholipids by HL activity, which is increased in IR/T2DM, results in disruption of particles with loss of CE and apoA-I. The decrease in HDL particles available for participation in RCT may be important to the atherogenicity of the dyslipidemia associated with T2DM [23, 42, 43, 48, 49].

Current Treatment Guidelines

In the setting of multifactorial risk reduction with statins and other lipid-lowering agents, antihypertensive therapies, and antihyperglycemic treatment strategies, cardiovascular disease rates are falling, yet remain higher for patients with diabetes mellitus than for those without [50•]. Most guidelines have recognized the significantly increased risk of ASCVD in people with diabetes mellitus, although not necessarily considering them to have CHD equivalence. In the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, which markedly altered approaches to lowering LDL-C in people at risk for CVD in the USA [51], diabetes was considered to be a high-risk category and treatment with high doses of potent statins recommended for secondary prevention and moderate- to high-dose treatments for those who have not had an event yet, depending on overall risk. The recently released 2015 ACC/AHA report [52] suggested that individuals with diabetes receive moderate-intensity statin therapy for adults 40–75 years, with high-intensity statin therapy considered for such individuals with a ≥7.5% estimated 10-year ASCVD risk or a prior CVD event. In adults with diabetes, who are <40 years of age or >75 years of age or who have a LDL of <70 mg/dL, it was recommended that health providers evaluate the potential for ASCVD benefits and for adverse effects and drug–drug interactions and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy [51]. Similar recommendations have been issued by the European Atherosclerotic Society (EAS), European Society of Cardiology (ESC) [53], and the European Association for the Study of Diabetes (EASD) [54]. Based on a recent European population study, ACC/AHA and ESC prevention guidelines often do not align at the individual level [55].

Preventive Measures

The development of T2DM is impacted significantly by diet, exercise habits, and weight control. Therefore, lifestyle interventions are key to any successful treatment program. Studies such as the Diabetes Prevention Program [56] showed that dietary interventions to reduce body weight by 6%, together with increased physical activity, can reduce the

incidence of T2DM in groups with impaired glucose tolerance by up to 58%. There is still much debate in the field regarding which diet strategy is most effective for both weight loss and reductions in CV risk, but caloric restriction should be part of any comprehensive nutritional plan for patients with T2DM. During active weight loss, exact composition, other than reductions in saturated fats, is less important than caloric restriction. During weight maintenance, people with diabetes need to restrict simple and low-fiber carbohydrates and should follow a balanced diet with low-sugar fruits, vegetables, fish, and poultry as the major sources of calories [57]. Salt restriction is also important in this population, where hypertension is common.

T2DM exert a greater negative impact on several CVD risk factors in women compared to men and this must be taken into account when treating each gender. This may, at least in part, account for the greater relative increase in coronary heart disease (CHD) risk observed in women with T2DM compared with their male counterparts [58, 59, 60, 61].

Glucose-lowering Agents

The effects of glucose-lowering agents on dyslipidemia are beyond the scope of the current review. Briefly, various treatments have been shown to have modest but positive lipid effects, including metformin, GLP1 receptor agonists, DPP-4 inhibitors, alfa-glucosidase inhibitors, colesevelam, and insulin [62•, 63, 64, 65, 66, 67, 68, 69]. Pioglitazone also has TG-lowering effects while rosiglitazone can increase TG levels [70]. Sulfonylureas can also have negative lipid effects [71, 72, 73, 74]. The SGLT2 inhibitors can lower TG and raise HDL but may also raise LDL-C levels slightly; in the case of empagliflozin, this has been shown to be mainly due to hemoconcentration [75, 76]. Importantly, recent studies have demonstrated positive CV outcomes with several antidiabetic agents, including pioglitazone [77], empagliflozin [78], liraglutide [79], and semaglutide [80] without a clear relationship to effects on lipid levels.

Lipid-lowering Agents

Statins—Statin therapy is the cornerstone of cardiovascular risk reduction in patients with T2DM [81] and is considered the first-line treatment for hyperlipidemia in all patients, including those with diabetes [82]. In a meta-analysis of 14 RCTs which included 18,686 patients with T2DM, statin monotherapy resulted in a 9% reduction in all-cause mortality and a 21% reduction in the incidence of major cardiovascular incidents per millimole per liter of LDL lowered [83]. It must be noted that the 2013 AHA/ACC guidelines for the treatment of cholesterol support the use of statins in several high-risk groups but do not support additional medications in combination with statins [51]. All other guidelines support the use of statins to reach targets and/or a 50% reduction in LDL-C, with addition of nonstatin agents varying by specific guidelines [52]. Statins lower LDL-C by inhibiting cholesterol biosynthesis, which by reducing hepatic cholesterol concentrations, leads to upregulation of hepatic LDL receptors and increased LDL particle clearance. In insulin-resistant individuals with dyslipidemia, statins may also reduce VLDL secretion and may reduce the hepatic assembly and secretion of apoB-containing lipoproteins. And may also increase LDL clearance [84, 85, 86].

There are several agents available for clinical use: lovastatin, fluvastatin, pravastatin, simvastatin, atorvastatin, rosuvastatin, and pitavastatin. These agents lower LDL-C by 18–55%, increase HDL-C by 5–15%, and reduce TG levels by 7–30% [84, 86].

A recent joint statement from the American Heart Association and the American Diabetes Association provided guidelines for those individuals with baseline T2DM and LDL-C levels less than 100 mg/dL. In these patients, the initiation of statins should be based on risk and clinical judgment. The committee suggested that in patients over the age of 40 years with the presence of at least one major CVD risk factor, a statin may be adequate [87].

The MRC/BHF HPS provided strong evidence supporting the benefit of statins in reducing the risk of CVD in individuals with T2DM and pre-existing occlusive arterial disease [88•]. In all statin trials, the diabetic subgroup had the most events and the most absolute benefit.

Ezetimibe: This was most recently demonstrated once again in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [89•]. This trial supported the hypothesis that lower LDL cholesterol targets may be important to reduce residual ASCVD risk in patients with diabetes mellitus and that additional benefit can be achieved with nonstatin drugs.

Fibrates: Fibrates have been used to lower elevated levels of TG and raise HDL-C levels for the past four decades. Early studies of fibrate monotherapy to reduce CVD events gave variable results [90] [91, 92]; there were varying numbers of people with T2DM in those trials. The two most recent trials with fenofibrate both focused on patients with T2DM. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial [93••], 9975 individuals with type 2 diabetes mellitus not on statin therapy were randomized to micronized fenofibrate vs placebo for 5 years. No effect of fenofibrate was seen on the primary outcome of coronary heart disease death or nonfatal myocardial infarction. In a post hoc analysis of participants with HDL-C <40 and TG >200 mg/dL, there was a 27% reduction in the primary endpoint in the group receiving fenofibrate. This group comprised approximately 20% of the FIELD population of the entire study population [94].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was a double 2 × 2 design to test standard vs intensive glycemic control [95], standard vs intensive blood pressure control [96], and fenofibrate vs placebo on a background of simvastatin therapy [97]. None of the three studies were positive; fenofibrate plus simvastatin did not lower the annual rate of the primary composite outcome of major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) compared to placebo plus simvastatin. However, a prespecified subgroup analysis [97] of patients defined as having dyslipidemia with TG levels in the upper tertile (>204 mg/dL) and HDL-C levels in the lower tertile (<34 mg/dL) had 29% fewer events than those without dyslipidemia. The dyslipidemic group comprised 17% of the total participants.

Importantly, post hoc analyses of the Helsinki Heart Study and the Bezafibrate Infarction Prevention Trial both showed marked benefits in groups with baseline TG levels greater than 200 mg/dL with or without low HDL-C levels. A study with a new fibrate, permafibrate, is

just starting and will enroll 10,000 participants all with TG levels >200 mg/dL and HDL-C <40 mg/dL. It will take several years to see the results.

Niacin: The discovery that niacin lowered cholesterol occurred over 60 years ago and in the 1970s, the Coronary Drug Project Niacin Arm showed a significant reduction in CVD events in men who had already survived events. In the ensuing years, niacin was used for treatment of hypertriglyceridemia and low HDL-C; in fact, it was the most potent HDL-raising drug available. It was also a mainstay of the treatment of patients with familial hypercholesterolemia in the prestatin era. Niacin has many side effects that are annoying but harmless (flushing, itching) but can also be hepatotoxic and can worsen pre-existing diabetes or convert individuals with prediabetes to full diabetes. Two recent studies, in which niacin was added to statin therapy, failed to show benefit over statin alone and confirmed the diabetogenic effects of niacin.

Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) [4] evaluated addition of niacin to intensive statin therapy (simvastatin plus ezetimibe if needed to maintain LDL of 40–80 mg/dL) in 3414 patients with established cardiovascular disease and low HDL cholesterol (median baseline HDL cholesterol of 35 mg/dL [0.91 mmol/L]). One third of the patients enrolled in the study had diabetes mellitus. No difference in the primary composite endpoint was observed despite increased mean HDL cholesterol from 35 to 42 mg/dL (0.91–1.09 mmol/L), lowering triglycerides from 164 to 122 mg/dL (1.85 to 1.38 mmol/L), and lowering LDL cholesterol from 74 to 62 mg/dL (1.92 to 1.61 mmol/L). The trial was stopped 18 months early, after a mean follow-up period of 3 years, for a lack of efficacy and an unexpected higher rate of ischemic strokes in the niacin group.

In the Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) [98], investigators included >8000 patients with diabetes mellitus (32.3% of the total study population) and compared extended-release niacin vs placebo on a background of statin therapy in high-risk patients with a previous vascular disease. No clinical benefit with niacin was observed in this population; likewise, the study was stopped early because of a significant increase in diabetes.

CETP Inhibitors: As described earlier, CETP plays a major role in the regulation of plasma HDL-C levels. Based on the knowledge that rodents, who lack CETP, have almost all their cholesterol in HDL and are resistant to atherosclerosis, and a small number of individual lacking CETP also have very high HDL-C levels, inhibition of (CETP) activity became a target for the pharmaceutical companies. Blocking the transfer of HDL-C to apoB lipoproteins was hypothesized to drive RCT more efficiently, avoiding the return of HDL-derived cholesterol to the arterial plaque by remnants and LDL. This could offer particular benefit to individuals with the IR/T2DM dyslipidemia, where increased TG-rich apoB lipoproteins stimulate CETP-mediated transfer of CE out of HDL [99, 100, 101, 102••]. Unfortunately, to date, three trials with CETP inhibitors (Illuminate [103], dal-Outcomes [104], and Accelerate [105••]) have failed and only one (Reveal; Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification, ClinicalTrials.gov Identifier:

NCT01252953) remains active. Thus, it remains to be demonstrated if raising HDL-C by inhibiting CETP will decrease the risk of CVD events [106].

PCSK9 Inhibitors: Serum proprotein convertase subtilisin kexin type 9 (PCSK9) binds to low-density lipoprotein receptors and targets them to the lysosome, along with LDL, instead of allowing them to recycle efficiently. This results to fewer LDL receptors on the surface of cells, particularly the liver, increasing serum LDL-C [107]. In response to a rapid series of preclinical studies (Horton; Seidah review) and population genetics (Cohn NEJM; Copenhagen), several companies developed monoclonal antibodies that bind PCSK9 in the circulation, rendering them unable to bind to the LDL receptor. Two fully human monoclonal antibodies to PCSK9, evolocumab and alirocumab, have shown the ability to reduce LDL levels between 50 and 70% in short-term studies [108••] and were approved by the FDA and the EMA. Secondary analyses of the OSLER and ODYSSEY LONG TERM studies published in 2015 demonstrated early evidence of improving patient outcomes by reducing the rate of major adverse cardiovascular events (MACE) compared to standard statin therapy [109•, 110•]. These studies raise optimism regarding several large CVD outcome studies now under way. Other monoclonal antibodies are being studied as are siRNAs and antisense molecules. As diabetics remain at the highest risk for having recurrent events, even on optimal lipid-altering therapies, the potency of the PCSK9 inhibitors may be a major advance in the treatment of individuals with T2DM.

Possible Future Treatments: Although detailed reviews of drugs in development are beyond the scope of this report, it is worth mentioning those with special relevance to individuals with IR/T2DM briefly. An antisense against apoCIII is in Phase 2–3 trials and has shown promise both in lowering plasma TG levels and in improving insulin sensitivity [111•]. 8-Hydroxy-2,2,14,14-tetramethylpentadecanedioic acid (ETC-1002) is a small molecule shown to modulate pathways of cholesterol, fatty acid, and carbohydrate metabolism in preclinical studies. In a single-center, double-blind, and placebo-controlled trial in 60 patients with T2DM, ETC-1002 monotherapy reduced total cholesterol, non-HDL-C, and LDL-C significantly compared with placebo but with no significant effect on triglyceride concentration or glycemia [112]. Saroglitazar, a dual proliferator-activated receptor-alpha/gamma agonist, which was approved in India in 2013, reduced plasma triglycerides, total cholesterol, non-HDL-C, VLDL cholesterol, HbA_{1c}, and fasting glucose levels in patients with T2DM [113]. Bariatric surgery may also improve some of the metabolic disturbances associated with T2DM.

Conclusions

Although several very recent studies indicate that glucose control, at least with some agents (repeat the four NEJM refs above) can provide protection from cardiovascular disease in patients with T2DM, these patients are still at increased risk. This population should have a comprehensive plan that includes lifestyle modifications and management of dyslipidemia with the goal of decreasing plasma LDL-C and apoB with statins and possibly ezetimibe [114••]. There are residual risks that remain after optimal statin therapy that may be addressed by adding treatments that elevate HDL and reduce TG levels such as fibrates and niacin, although proof that these agents reduce CVD is limited. Novel treatments are on the

horizon; we await the outcome data of the ongoing studies on the effects of CETP and PCSK9 inhibition [115].

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Geiss LS, Wang J, Cheng YJ, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980–2012. JAMA. 2014; 312(12):1218–26. [PubMed: 25247518]
2. National Diabetes Statistics Report: estimates of diabetes and its burden in the United States, 2014. Centers for Disease Control and Prevention; 2014.
3. World Health Organization. Cardiovascular diseases (CVDs). http://www.who.int/mediacentre/factsheets/fs317/en/
4. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011; 365(24):2255–67. [PubMed: 22085343]
5. Gotto AM Jr, Pownall HJ, Havel RJ. Introduction to the plasma lipoproteins. Methods Enzymol. 1986; 128:3–41. [PubMed: 3523141]
6. Ginsberg HN. Lipoprotein physiology. Endocrinol Metab Clin N Am. 1998; 27(3):503–19.
7. Lamarche B, Couture P. Dietary fatty acids, dietary patterns, and lipoprotein metabolism. Curr Opin Lipidol. 2016; 26(1):42–7.
8. Ginsberg HN, Fisher EA. The ever-expanding role of degradation in the regulation of apolipoprotein B metabolism. J Lipid Res. 2009; 50(Suppl):S162–6. [PubMed: 19050312]
9. Tomkin GH, Owens D. Abnormalities in Apo B-containing lipoproteins in diabetes and atherosclerosis. Diabetes Metab Res Rev. 2001; 17:27–43. [PubMed: 11241889]
10. Havel RJ. Lipid transport function of lipoproteins in blood plasma. Am J Phys. 1987; 253:E1–5.
11. de Man FH, Cabezas MC, Van Barlingen HHJJ, Erkelens DW, De Bruin TWA. Triglyceride-rich lipoproteins in non-insulin dependent diabetes mellitus:post-prandial metabolism and relation to premature atherosclerosis. Eur J Clin Investig. 1996; 26:89–108. [PubMed: 8904518]
12. Goldberg IJ. Clinical review 124, diabetic dyslipidemia: causes and consequences. J Clin Endocrinol Metab. 2001; 86:965–71. [PubMed: 11238470]
13. Mahley RW, Ji ZS. Remnant lipoprotein metabolism: key pathways involving cell-surface heparan sulfate proteoglycans and apolipoprotein. J Lipid Res. 1999; 40:1–16. [PubMed: 9869645]
14. Phillips C, Bennett A, Anderton K. Intestinal rather than hepatic microsomal triglyceride transfer protein as a cause of postprandial dyslipidemia in diabetes. Metabolism. 2002; 51:847–52. [PubMed: 12077729]
15. Phillips C, Owens D, Collins P, Tomkin GH. Microsomal triglyceride transfer protein: does insulin resistance play a role in the regulation of chylomicron assembly? Atherosclerosis. 2002; 160:355–60. [PubMed: 11849658]
16. Haidari M, Leung N, Mahbub F, et al. Fasting and postprandial overproduction of intestinally derived lipoproteins in an animal model of insulin resistance. J Biol Chem. 2002; 277(35):31646–55. [PubMed: 12070142]
17. Dressel U, Allen TL, Pippal JB, Rohde PR, Lau P, Muscat GEO. The peroxisome proliferator-activated receptor β/δ agonist, GW501516, regulates the expression of genes involved in lipid catabolism and energy uncoupling in skeletal muscle cells. Mol Endocrinol. 2003; 17:2477–93. [PubMed: 14525954]
18. Xiao C, Dash S, Morgantini C, Adeli K, Lewis GF. Gut peptides are novel regulators of intestinal lipoprotein secretion: experimental and pharmacological manipulation of lipoprotein metabolism. Diabetes. 2015; 64(7):2310–8. [PubMed: 26106188]

19. Adeli K, Lewis GF. Intestinal lipoprotein overproduction in insulin-resistant states. Curr Opin Lipidol. 2008; 19:221–8. [PubMed: 18460911]
20. Brunzell, JD. Source Gene Reviews. 2015. Familial lipoprotein lipase deficiency.
21. Cohn JS, Patterson BW, Uffelman KD, Davignon J, Steiner G. Rate of production of plasma and very-low-density lipoprotein (VLDL) apolipoprotein C-III is strongly related to the concentration and level of production of VLDL triglyceride in male subjects with different body weights and levels of insulin sensitivity. Journal of Clinical Endocrinology & Metabolism. 2004; 89:3949–55. [PubMed: 15292332]
22. Nagashima K, Lopez C, Donovan D, et al. Effects of the PPAR agonist pioglitazone on lipoprotein metabolism in patients with type 2 diabetes mellitus. JCI. 2005; 115:1323–32. [PubMed: 15841215]
23. Ginsberg HN, Zhang Y-L, Hernandez-Ono A. A metabolic syndrome: focus on dyslipidemia. Obesity. 2006; 14(Suppl):41S–9S. [PubMed: 16642962]
24. Zhang Y-L, Hernandez-Ono A, Ko C, Yasunaga K, Huang L-S, Ginsberg HN. Regulation of hepatic apolipoprotein B-lipoprotein assembly and secretion by the availability of fatty acids 1: differential effects of delivering fatty acids via albumin or remnant-like emulsion particles. J Biol Chem. 2004; 279:19362–74. [PubMed: 14970200]
25. Lewis GF, Uffelman KD, Szeto LW, Weller B, Steiner G. Interaction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans. J Clin Invest. 1995; 95:158–66. [PubMed: 7814610]
26. Cooper AD. Hepatic uptake of chylomicron remnants. J Lipid Res. 1997; 38(11):2173–92. [PubMed: 9392416]
27. Wu X, Sakata N, Dixon JL, Ginsberg HN. Exogenous VLDL stimulates apolipoprotein B from HepG2 cells by both pre- and post-translational mechanisms. J Lipid Res. 1994; 35:1200–10. [PubMed: 7964181]
28. Grimaldi PA, Teboul L, Inadera H, Gaillard D, Amri E-Z. Transdifferentiation of myoblasts to adipoblasts: triggering effects of fatty acids and thiazolidinediones. Prostaglandins Leukot Essent Fatty Acids. 1997; 57:71–5. [PubMed: 9250611]
29. Melish J, Le NA, Ginsberg H, Steinberg D, Brown WV. Dissociation of apoprotein B and triglyceride production in very-low-density lipoproteins. Am J Phys. 1980; 239(5):E354–62.
30. Ma W, Wu JH, Wang Q, et al. Prospective association of fatty acids in the de novo lipogenesis pathway with risk of type 2 diabetes: the Cardiovascular Health Study. Am J Clin Nutr. 2015; 101(1):153–63. [PubMed: 25527759]
31. Adiels M, Boren J, Caslake MJ, et al. Overproduction of VDLD1 driven by hyperglycemia is a dominant feature of diabetic dyslipidemia. Arterioscler Thromb Vasc Biol. 2005; 25:1697–703. [PubMed: 15947244]
32. Keeny, SJ., Aubert, RE., Geiss, LS. Prevalence and incidence of insulin-dependent diabetes in America. NIH. National Institute of Health; 1995.
33. Adiels M, Olofsson SO, Taskinen MR, Boren J. Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. Artheroscler Thromb Vasc Biol. 2008; 28:1225–36.
34. Sharma V, Forte TM, Ryan RO. Influence of apolipoprotein AVon the metabolic fate of triacylglycerol 1. Curr Opin Lipidol. 2013; 24(2):153–9. [PubMed: 23241513]
35. Robciuc MR, Maranghi M, Lahikainen A, et al. Angptl3 deficiency is associated with increased insulin sensitivity, lipoprotein lipase activity, and decreased serum free fatty acids. Arterioscler Thromb Vasc Biol. 2013; 33(7):1706–13. [PubMed: 23661675]
36. Kurra S, Ballantyne CM. Special patient populations: diabetes and metabolic syndrome. In Clinical lipidology: a companion to braunwald's heart disease. Elsevier Health Sciences. 2009:443–462.
37. Berneis KK, Krauss RM. Metabolic origins and clinical significance of the LDL heterogeneity. J Lipid Res. 2009; 43:1363–79.
38. Mello AP, da Silva IT, Abdalla DS, Damasceno NR. Electronegative low-density lipoprotein: origin and impact on health and disease. Atherosclerosis. 2011; 215:257–65. [PubMed: 21292266]
39. Rizzo M, Berneis K. Low-density lipoprotein size and cardiovascular risk assessment. QJM. 2006; 99:1–14. [PubMed: 16371404]

40. Timmins JM, Lee JY, Boudyguina E, et al. Targeted inactivation of hepatic Abca1 causes profound hypoalphalipoproteinemia and kidney hypercatabolism of apoA-1. J Clin Invest. 2005; 115:1333–42. [PubMed: 15841208]
41. Chahil TJ, Ginsberg HN. Diabetic dyslipidemia. Endocrinol Metab Clin N Am. 2006; 35:491–510.
42. Lewis GF, Radar DJ. New insights into the regulation of HDL. Metabolism and reverse cholesterol transport. Circ Res. 2005; 96:1221–32. [PubMed: 15976321]
43. Borggreve SE, De Vries R, Dullaart RP. Alterations in high-density lipoprotein metabolism and reverse cholesterol transport in insulin resistance and type 2 diabetes mellitus: role of lipolytic enzymes, lecithin: cholesterol acyltransferase and lipid transfer proteins. Eur J Clin Investig. 2003; 33:1051–69. [PubMed: 14636288]
44. Horowitz BS, Goldberg IJ, Merab J, Vanni T, Ramakrishnan R, Ginsberg HN. Increased plasma and renal clearance of an exchangeable pool of apolipoprotein A-I in subjects with low levels of high density lipoprotein cholesterol. J Clin Invest. 1993; 91:1743–52. [PubMed: 8473514]
45•. Xiao C, Dash S, Morgantini C, Hegele RA, Lewis GF. Pharmacological targeting of the atherogenic dyslipidemia complex: the next frontier in CVD prevention beyond lowering LDL cholesterol. Diabetes. 2016; 65(7):1767–78. A thourough desciption on the regulatory effect of GLP-1 and GLP-2 on intestinal lipoprotein secretion and postprandial lipemia. [PubMed: 27329952]
46. Brinton EA, Eiseberg S, Breslow JL. Human HDL cholesterol levels are determined by apoA-I fractional catabolic rate, which correlates inversely with estimate of HDL particle size. Arterioscler Thromb. 1994; 14:707–20. [PubMed: 8172849]
47. Liu J, Hernandez-Ono A, Graham MJ, Galton VA, Ginsberg HN. Type 1 deiodinase regulates ApoA-I gene expression and ApoA-I synthesis independent of thyroid hormone signaling. Arterioscler Thromb Vasc Biol. 2016; 36(7):1356–66. [PubMed: 27150392]
48. Riemens S, van Tol A, Sluiter W, Dullaart R. Elevated plasma cholesteryl ester transfer in NIDDM: relationships with apolipoprotein B-containing lipoproteins and phospholipid transfer protein. Atherosclerosis. 1998; 140:71–9. [PubMed: 9733217]
49. Deeb SS, Zambon A, Carr MC. Hepatic lipase and dyslipidemia: interactions among genetic variants, obesity, gender, and diet. J Lipid Res. 2003; 44:1279–86. [PubMed: 12639974]
50•. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus—mechanisms, management, and clinical considerations. Circulation. 2016; 133(24): 2459–502. This review points out to the mechanisms, history, controversies, and pharmacological agents for cardiovascular management in the patient with diabetes mellitus. [PubMed: 27297342]
51. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. :2013.
52. Drozda JP Jr, Ferguson TB Jr, Jneid H, et al. 2015 ACC/AHA focused update of secondary prevention lipid performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. J Am Coll Cardiol. 2016; 67(5):558–87. [PubMed: 26698405]
53. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis. :53. [PubMed: 28011257]
54. Ryden L, Standl E, Bartnik M. for the Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. Eur Heart J. 2007; 28:88–136. [PubMed: 17220161]
55. Pavlovic J, Greenland P, Deckers JW, et al. Comparison of ACC/AHA and ESC guideline recommendations following trial evidence for statin use in primary prevention of cardiovascular disease: results from the population-based Rotterdam Study. JAMA Cardiol. 2016

56. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2016; 346(6):393–403.
57. American Diabetes Association. Standards of medical care in diabetes—2016. Diabetes Care. 2016; 39(suppl 1)
58. Siegel RD, Cupples A, Schaefer EJ, Wilson PWF. Lipoproteins, apolipoproteins, and low-density lipoprotein size among diabetics in the Framingham Offspring Study. Metabolism. 1996; 45(10): 1267–72. [PubMed: 8843183]
59. Howard BV, Cowan LD, Go O, Welty TK, Robbins DC, Lee ET. Adverse effects of diabetes on multiple cardiovascular disease risk factors in women. Diabetes Care. 1998; 21:1258–65. [PubMed: 9702430]
60. Juutilainen A, Kortelainen S, Lehto S, et al. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care. 2004; 27:2898–904. [PubMed: 15562204]
61. Haffner SM, Miettinen H, Stern MP. Relatively more atherogenic coronary heart disease risk factors in prediabetic women than in prediabetic men. Diabetologia. 1997; 40:711–7. [PubMed: 9222652]
62•. Rosenblit PD. Common medications used by patients with type 2 diabetes mellitus: what are their effects on the lipid profile? Cardiovasc Diabetol. 2016; 15(95) An overview on type 2 diabetes mellitus treatment effects on lipid profile and their overall potential impact on ASCVD risk.
63. Choe EY, Cho Y, Choi Y, et al. The effect of DPP-4 inhibitors on metabolic parameters in patients with type 2 diabetes. Diabetes Metab J. 2014; 38(3):211–9. [PubMed: 25003075]
64. Harris KB, McCarty DJ. Efficacy and tolerability of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus. Ther Adv Endocrinol Metab. 2015; 6(1):3–18. [PubMed: 25678952]
65. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metab. 2016; 18(8):783–94. [PubMed: 27059700]
66. Rosenthal N, Meininger G, Ways K, et al. Canagliflozin: a sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes mellitus. Ann N Y Acad Sci. 2016; 1358:28–43.
67. Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S. Study 05 Group. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care. 2015; 38(3):365–72. [PubMed: 25592197]
68. Rosenstock J, Rigby SP, Ford DM, Tao B, Chou HS. The glucose and lipid effects of colesevelam as monotherapy in drug-naïve type 2 diabetes. Horm Metab Res. 2014; 46(5):348–53. [PubMed: 24356792]
69. Monami M, Vitale V, Ambrosio ML, et al. Effects on lipid profile of dipeptidyl peptidase 4 inhibitors, pioglitazone, acarbose, and sulfonylureas: meta-analysis of placebo-controlled trials. Adv Ther. 2012; 29(9):736–46. [PubMed: 22923161]
70. Doggrell SA. Clinical trials with thiazolidinediones in subjects with type 2 diabetes—is pioglitazone any different from rosiglitazone? Expert Opin Pharmacother. 2008; 9(3):405–20. [PubMed: 18220491]
71. Chiquette E, Ramirez G, Defronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. Arch Intern Med. 2004; 164(19):2097–104. [PubMed: 15505122]
72. Yau H, Rivera K, Lomonaco R, Cusi K. The future of thiazolidinedione therapy in the management of type 2 diabetes mellitus. Curr Diab Rep. 2013; 13(3):329–41. [PubMed: 23625197]
73. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2016 executive summary. Endocr Pract. 2016; 22(1):84–113. [PubMed: 26731084]
74. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. JAMA. 2016; 316(3):313–24. [PubMed: 27434443]
75. Scheen AJ. SGLT2 inhibitors: benefit/risk balance. Curr Diab Rep. 2016; 16(10):92. [PubMed: 27541294]

76. Wilding JP, Rajeev SP, DeFronzo RA. Positioning SGLT2 inhibitors/incretin-based therapies in the treatment algorithm. Diabetes Care. 2016; 39(supp2:S):154–64.

77. Kernan WA, Viscoli CM, Furie KL, Winder TR. IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. NE J Med. 2016; 374(14):1321–31.

78. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373(22):2117–28. [PubMed: 26378978]

79. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016; 375(4):311–22. [PubMed: 27295427]

80. Marso SP, Bain SC, Consoli A, Eliaschewitz FG. SUSTAIN-6 investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. NE J Med. 2016

81. Mooradian AD. Cardiovascular disease in type 2 diabetes mellitus: current management guidelines. Arch Intern Med. 2003; 163(1):33–40. [PubMed: 12523914]

82. Warraich HJ, Wong ND, Rana JS. Role for combination therapy in diabetic dyslipidemia. Curr Cardiol Rep. 2015; 17(5):32. [PubMed: 25894802]

83. Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008; 371(9607): 117–25. [PubMed: 18191683]

84. National Cholesterol Education Program. Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001; 285(19):2486–97. [PubMed: 11368702]

85. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2007; 30(Suppl):S4–S41. [PubMed: 17192377]

86. Ginsberg HN. Efficacy and mechanism of action of statins in the treatment of diabetic dyslipidemia. J Clin Endocrinol Metab. 2006; 91:383–92. [PubMed: 16291700]

87. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus. A scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care. 2007; 30:162–72. [PubMed: 17192355]

88•. Collins R, Armitage J, Parish S, HPSCG. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5,963 people with diabetes. Lancet. 2005; 361:2005–16. A randomized trial of the effect of simvastatin vs placebo in patients with diabetes that provides direct evidence that cholesterol-lowering therapy is beneficial for these people even if they do not show manifestation of coronary disease or high cholesterol concentrations.

89•. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015; 372(25):2387–97. A comparison of the combination of simvastatin and ezetimibe with simvastatin and placebo on the cardiovascular outcome in patients with acute coronary syndromes. [PubMed: 26039521]

90. Frick MH, Elo MO, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. NE J Med. 1987; 317:1237–45.

91. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999; 341(6): 410–8. [PubMed: 10438259]

92. Bezafibrate Infarction Prevention (BIP) study1. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. Bezafibrate Infarction Prevention (BIP) study. Circulation. 2000; 102(1):21–7. [PubMed: 10880410]

93••. Keech A, Simes RJ, Barter P. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005; 366:1849–61. A control trial study of individuals with type 2 diabetes mellitus not on statin therapy, randomized to take fenofibrate vs placebo for 5 years to assess the effect of fenofibrate on cardiovascular disease events in these patients. [PubMed: 16310551]

94. Scott R, O'Brien R, Fulcher G, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetes Care. 2009; 32:493–8. [PubMed: 18984774]

95. Anderson RT, Narayan KM, Feeney P, et al. Effect of intensive glycemic lowering on health-related quality of life in type 2 diabetes: ACCORD trial. Diabetes Care. 2011; 34(4):807–12. [PubMed: 21346183]
96. Cushman WC, Evans GW, et al. Accord Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010; 362(17):1575–85. [PubMed: 20228401]
97. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010; 362(17):1563–74. [PubMed: 20228404]
98. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014; 371(3):203–12. [PubMed: 25014686]
99. Mann CJ, Yen FT, Grant AM, Bihan BE. Mechanisms of plasma cholesteryl ester transport in hypertriglyceridemia. J Clin Invest. 1991; 88:2059–66. [PubMed: 1752964]
100. Tall AR, Granot E, Tabas I, et al. Accelerated transfer of cholesteryl esters in dyslipidemic plasma: role of cholesteryl ester transfer protein. J Clin Invest. 1987; 79:1217–25. [PubMed: 3558822]
101. Deckelbaum RJ, Granot E, Oschry Y, Rose L, Eisenberg S. Plasma triglyceride determines structure-composition in low and high density lipoproteins. Arteriosclerosis. 1984; 4:225–31. [PubMed: 6712536]
102••. Reyes-Soffer G, Millar JS, Ngai C, et al. Cholesteryl ester transfer protein inhibition with anacetrapib decreases fractional clearance rates of high-density lipoprotein apolipoprotein A-I and plasma cholesteryl ester transfer protein. Artheroscler Thromb Vasc Biol. 2016:115. A study on the effects of CETP inhibition on the kinetics of CETP in humans.
103. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007; 357(21):2109–22. [PubMed: 17984165]
104. Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. NE J Med. 2012; 367(22):2089–99.
105••. Nicholls SJ, Lincoff AM, Barter PJ, et al. Assessment of the clinical effects of cholesteryl ester transfer protein inhibition with evacetrapib in patients at high-risk for vascular outcomes: rationale and design of the ACCELERATE trial. Am Heart J. 2015; 170(6):1061–9. A contol trial study on 12,092 individual with high-risk vascular disease, randomized to take evacetrapib or placebo in addition to standard medical therapy and to acess its effect on the cardiovascular morbidity and mortality. [PubMed: 26678626]
106. Rader DJ, Tall AR. The not-so-simple HDL story: is it time to revise the HDL cholesterol hypothesis? Nat Med. 2012; 18(9):1344–6. [PubMed: 22961164]
107. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol. 2012; 59(25):2344–53. [PubMed: 22463922]
108••. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. Ann Intern Med. 2015; 163(1):40–51. A phase 3 randomized controlled trial to compare treatment of hypercholesterolemia with and without PCSK9 antibodies which has proven PCSK9 inhibitors to be safe and effective for adults with dyslipidemia. [PubMed: 25915661]
109•. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015; 372(16):1489–99. A randomized trial involving 2341 patients at high risk for cardiovascular events and at maximum dose of statin randomly assigned to receive alirocumab over a period of 78 weeks. [PubMed: 25773378]
110•. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015; 372(16):1500–9. This study points to the long-term effect of evolocumab plus standard therapy, as compared with standard therapy alone on reducing LDL cholesterol levels and the incidence of cardiovascular events. [PubMed: 25773607]

111•. Yang X, Lee SR, Choi YS, et al. Reduction in lipoprotein-associated apoC-III levels following volanesorsen therapy: phase 2 randomized trial results. J Lipid Res. 2016; 57(4):706–13. A study on the effects of volanesorsen (an antisense drug that targets apoC3 mRNA) vs placebo in patients with hypertriglyceridemia. [PubMed: 26848137]

112. Gutierrez MJ, Rosenberg NL, Macdougall DE, et al. Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol. 2014; 34(3):676–83. [PubMed: 24385236]

113. Jani RH, Pai V, Jha P, et al. A multicenter, prospective, randomized, double-blind study to evaluate the safety and efficacy of Saroglitazar 2 and 4 mg compared with placebo in type 2 diabetes mellitus patients having hypertriglyceridemia not controlled with atorvastatin therapy (PRESS VI). Diabetes Technol Ther. 2014; 16(2):63–71. [PubMed: 24138536]

114••. Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2016 This study points to the association between weight loss and the incidence of cardiovascular disease in people with type 2 diabetes from the LOOK AHEAD study after ~10-year follow-up.

115. Szalat A, Durst R, Leitersdorf E. Managing dyslipidaemia in type 2 diabetes mellitus. Best Pract Res Clin Endocrinol Metab. 2016; 30(3):431–44. [PubMed: 27432076]