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Treatment of Dyslipidemia in Diabetes: Recent Advances and Remaining Questions

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Abstract
Purpose of Review This article reviews current knowledge concerning diabetic dyslipidemia and cardiovascular disease (CVD). It reviews strategies to reduce diabetes-associated CVD, including reducing low-density lipoprotein levels, lowering triglycerides, and increasing high-density lipoproteins (HDL). Special considerations, such as the multifactorial chylomicronemia syndrome and partial lipodystrophy, and the role of glucose-lowering strategies in the management of diabetic dyslipidemia are discussed.
Recent Findings The strongest evidence to date for reducing CVD in diabetes comes from the use of statins. While triglyceride lowering remains inconclusive, an ongoing trial might provide some finality to this question. The role of increasing HDL remains elusive, and HDL cholesterol appears to be an unsatisfactory metric for monitoring therapy.
Summary The use of statins offers the best current way to reduce diabetes-associated CVD. However, several novel and promising approaches for the management of diabetic dyslipidemia aimed at reducing CVD are in the pipeline.

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Introduction

Type 2 diabetes is a common cause of premature coronary artery disease and stroke [1]. Conversely, the most common cause of morbidity and mortality in type 2 diabetes is premature cardiovascular disease (CVD). Moreover, the risk of CVD is increased well before the onset of overt diabetes, likely due to the existence of the metabolic syndrome, which often precedes the onset of hyperglycemia. Type 1 diabetes also is characterized by an increased risk of developing clinical CVD and death from CVD [2, 3], especially in the presence of hypertension and renal disease [4].

The metabolic syndrome is characterized by the presence of many cardiovascular risk factors such as dyslipidemia, hypertension, visceral adiposity, inflammation, and a predisposition to thrombosis; the presence of diabetes appears to impart a greater CVD risk than risk factors alone. Many strategies to reduce CVD risk in people with diabetes have been tried through the years. One of the least successful has been tight glycemic control, which nonetheless clearly is effective in preventing microvascular complications of diabetes [5]. Several large clinical trials have failed to demonstrate a benefit of glycemic control on clinical CVD events (reviewed in [5–7]), other than some long-term benefits of tight glycemic control in type 1 diabetes [8] and when treatment was started early in the course of type 2 diabetes [9], or in patients without

evidence of extensive atherosclerosis [5, 10]. Newer drugs that do provide CVD benefit might operate via mechanisms exclusive of blood sugar reduction. By far the most successful strategy to date has relied on management of diabetic dyslipidemia.

Dyslipidemia in Diabetes

In type 2 diabetes and the metabolic syndrome, dyslipidemia is characterized by the presence of hypertriglyceridemia, normal to mildly elevated levels of LDL cholesterol, with increased numbers of small dense LDL particles [11], and low HDL cholesterol levels, with variable changes in HDL composition [12, 13]. The concentration of apoB, which reflects the number of atherogenic lipoprotein particles [VLDL, remnant particles, LDL and Lp(a)], is also increased. Moreover, postprandial lipemia—the increase in chylomicrons and chylomicron remnants—is also increased in these patients [14]. These abnormalities can be modulated by the presence of genetic forms of dyslipidemia, lifestyle measures such as diet and exercise, the nature and extent of hyperglycemia management, and the presence of complications such as nephropathy.

The situation is different in type 1 diabetes, in which hypertriglyceridemia is characteristic of the untreated or poorly treated state, when HDL cholesterol levels also can be low [15, 16]. Although HDL cholesterol levels tend to be normal or even elevated in type 1 diabetic subjects under good glycemic control [17, 18], this increased HDL cholesterol does not always appear to provide CVD protection [19, 20]. The presence of renal complications can modulate plasma lipids and lipoproteins, especially the presence of the nephrotic syndrome, and lead to a similar lipid profile as seen with type 2 diabetes.

This article will not review the pathogenesis of diabetic dyslipidemia and mechanisms by which it leads to atherosclerosis, which have been reviewed elsewhere [7, 21]. Rather, the focus will be on management, especially drug treatment.

Statins

The major effect of statins is to lower LDL levels by inhibiting the rate-limiting enzyme in cholesterol synthesis, HMGCoA reductase, leading to increased hepatic expression of LDL receptors. Despite elevations of LDL cholesterol not being a major feature of diabetic dyslipidemia, to date statins have proven to be the most effective way of reducing CVD morbidity and mortality in type 2, and likely even type 1 diabetes. Early studies such as the Heart Protection Study (HPS), a large secondary prevention study that included subjects with diabetes, comparing simvastatin 40 mg versus placebo [22] and the Collaborative Atorvastatin Diabetes Study (CARDS), a primary prevention trial in which atorvastatin 10 mg was compared with placebo exclusively in people with diabetes [23], demonstrated a beneficial effect of statins on CVD endpoints. Subsequent studies have confirmed and extended these findings. Meta-analysis of 14 statin trials that included nearly 20,000 people with type 2 diabetes demonstrated that a statin-induced reduction of LDL cholesterol by approximately 40 mg/dL was associated with an approximately 20% reduction in CVD events and a 10% reduction in mortality [24]. Meta-analysis also showed that statins diminished CVD events and mortality in a much smaller number of subjects with type 1 diabetes [24]. However, more recently, statin use has been shown to increase the incidence of diabetes; it is estimated that for every 1 mM reduction in LDL (~ 40 mg/dL), conversion to diabetes is increased by approximately 10%, especially in subjects at high risk of diabetes, for example those with the metabolic syndrome [25]. Whether a similar increase in diabetes may also occur with proprotein convertase subtilisin/kexin type 9 (PCSK9), inhibition is unclear as genetic studies have associated LDL-lowering PCSK9 mutations with more diabetes [26], while the recently completed Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial did not find a statistically significant increase in new-onset diabetes with PCSK9 antibody treatment [27•]. The mechanism by which statins increase the risk of diabetes remains unclear, but a recent analysis in the Netherlands showed reduced diabetes in patients with familial hypercholesterolemia [28]. This suggests that increased islet cell LDL receptors might increase toxicity. Nonetheless, it has been estimated that the benefit of statins on CVD event and mortality far exceeds the downside of developing diabetes [25]. As a result of these findings, statin therapy has become a mainstay of primary and secondary CVD prevention in people with diabetes, especially type 2. Statin use in type 1 diabetes will be discussed in more detail later.

Other Modalities of LDL Lowering

The first clinical trial to demonstrate a benefit of LDL lowering was the Lipid Research Clinics Trial that used a bile acid binding resin. Bile acid sequestrants are much less effective at LDL lowering than statins, averaging around a 15% reduction. Moreover, compliance is poor with cholestyramine and colestipol, although less so with the newer agent, colesevelam [29]. Their main use in diabetes these days is in patients with statin intolerance, or in combination with a statin. However, all bile acid sequestrants increase plasma triglyceride levels [30], which often are elevated as part of the diabetic dyslipidemia phenotype. This adverse effect is offset by a modest benefit in reducing HbA1C and glycemic control [29].

Ezetimibe lowers LDL cholesterol by inhibiting gut cholesterol absorption at the level of NPC1L1 [31]. It too is less effective than statins, resulting in average LDL cholesterol lowering of 18–25% [32, 33]. However, this amount of LDL reduction is equivalent to or better than a threefold increase in statin dose. The major use of ezetimibe in diabetes is for statin-intolerant patients or in combination with statins to achieve greater LDL reduction. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) secondary prevention study, which compared statin alone versus statin plus ezetimibe, the strongest benefit of ezetimibe addition was in subjects with diabetes [34]. This provocative finding, which has not been confirmed in other studies, has led some physicians to consider its use as an add-on to statins for the prevention of CVD primarily in patients with diabetes, especially in those whose LDL has not reached levels than are associated with atherosclerosis plaque regression (less than 70 mg/dL).

The most exciting advance in cholesterol lowering therapy has been the recent availability of the PCSK9 antibodies. They lower LDL cholesterol to unprecedented levels, especially when used in combination with statins and/or ezetimibe [27•, 35, 36]. The first clinical trial to demonstrate a beneficial effect on CVD clinical endpoints, the FOURIER trial [27•], was published recently and included some patients with diabetes. However, these antibodies need to be injected every 2 or 4 weeks and are extremely expensive, and much more data is required concerning their use in people with diabetes. Moreover, some health insurance companies have limited prescription of PCSK9 antibodies to cardiologists, endocrinologists, and lipidologists.

Triglyceride Lowering in Diabetes

Despite the major reduction in CVD risk that occurs with the use of statins and other measures to lower LDL cholesterol, significant residual risk remains in subjects with diabetes. Some of this residual risk may be attributable to hypertriglyceridemia, which is a CVD risk factor in the general population, although the relationship weakens when taking into account confounding variables [37]. Since one of the major components of diabetic dyslipidemia is hypertriglyceridemia, triglyceride lowering would seem to be a logical way to reduce the risk of CVD in diabetes, although the mechanism by which hypertriglyceridemia is involved in the pathogenesis of atherosclerosis remains unclear [38]. Although lifestyle measures such as weight loss and exercise result in triglyceride lowering, studies to date have not conclusively demonstrated a CVD benefit. Fibrates, which are PPARα agonists and increase fatty acid oxidation, effectively lower plasma triglyceride levels. Several studies have demonstrated a benefit of fibrates on CVD events when used either alone or in combination with statins, although the benefit was only seen after subgroup analysis and was confined to individuals who were hypertriglyceridemic to start with and/or who also had reduced levels of HDL cholesterol [39–42]. This includes the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-LIPID trial, which was confined to subjects with diabetes [40]. Unfortunately, no fibrate studies to date have solely studied hypertriglyceridemic subjects, although a clinical trial, Prominent, using a novel selective peroxisome proliferator-activated receptor α modulator (K-877) that possesses unique PPARα activity and selectivity [43] is currently underway in individuals with hypertriglyceridemia and diabetes.

Niacin also lowers plasma triglyceride levels, in addition to lowering LDL cholesterol and apoB and increasing HDL cholesterol. However, it also increases insulin resistance, which has limited its use in people with diabetes. Despite long-term data in the pre-statin era showing that niacin reduced CVD events and mortality in hypercholesterolemic subjects [44], two recent studies with niacin in non-diabetic subjects who were on statins failed to show a beneficial effect on CVD endpoint [45, 46]. This has further limited enthusiasm for its use in diabetic dyslipidemia.

Omega-3 fatty acids also are of value in lowering elevated plasma triglyceride levels. Other than in a single clinical trial that showed a reduction in the cumulative incidence of major coronary events in a subgroup of subjects with TG ≥ 150 mg/dL and HDL-C < 40 mg/dL [47], the benefits of its use appears to be a reduction in the incidence of sudden death [48]. Although most meta-analyses show little if any beneficial effect, this may relate to inadequate doses of omega-3 fatty acids being administered [48]. Several CVD outcomes trials with omega-3 fatty acids are in progress.

There has been considerable recent interest in the role of apoC-III in hypertriglyceridemia and CVD. Genetic studies have shown that individuals with loss of function mutations in the apoC-III gene have lower triglyceride levels and CVD incidence than those without these mutations [49–51]. As a result, several pharmaceutical and biotechnology companies are developing strategies to lower apoC-III levels and one of these treatments, an anti-sense oligonucleotide, reduces triglyceride levels in patients with severe hypertriglyceridemia who are at risk of pancreatitis [52••]. In another small study, this therapy was also associated with improved insulin sensitivity [53]. Thus, future approaches to triglyceride lowering may include apoC-III lowering, and it is clear that further information regarding triglyceride lowering in diabetes is sorely needed (see later).

HDL and Diabetes

Diabetic dyslipidemia is characterized by reduced levels of HDL cholesterol, which is accompanied by several

described changes in HDL composition and function [12, 13]. HDL facilitates reverse cholesterol transport, the release of cholesterol from non-hepatic cells such as macrophages within atherosclerotic lesions, and allows cholesterol return to the liver. However, the levels of HDL cholesterol in humans do not correlate with changes in cholesterol balance [54]. HDL also has anti-oxidant and anti-inflammatory properties and can reduce endothelial damage and thrombosis [55]. All of these properties should be of value in reducing atherosclerotic CVD. As a result, strategies to increase HDL cholesterol were widely touted as a rational approach to reduce the residual risk that remains after statin treatment. However, recent events had dampened enthusiasm for raising HDL cholesterol. First, genetic studies have shown that some mutations that are associated with increased HDL cholesterol levels are not associated with reduced CVD risk [56, 57]. Second, clinical trials that have used strategies to raise HDL cholesterol with either CETP inhibitors [58] or niacin [45, 46] in cohorts without diabetes failed to show a benefit on CVD, despite also decreasing LDL cholesterol. Moreover, measures of HDL function such as cholesterol efflux capacity from macrophages have been shown to be a better predictor of prevalent and incident CVD than measurement of HDL cholesterol or its major apolipoprotein, apoA-I [59, 60]. This has resulted in questions regarding whether HDL function could be a better metric for assessing CVD risk, especially in response to interventions [61, 62]. Nonetheless, in most situations, HDL cholesterol adds to risk evaluation and is still included in all risk calculators.

Recent pharmacologic and genetic data have highlighted our ignorance of HDL biology [63]. Although deficiency [64, 65] or overexpressing [66, 67] apoA-I has clearly shown a reduction or acceleration of atherosclerosis respectively in mice, infusion of recombinant HDL or apoA-I did not reduce atheroma volume detected by IVUS in subjects with acute coronary syndrome [68]. Thus, new thinking is needed regarding strategies to take advantage of HDL's potentially anti-atherosclerotic properties.

Effect on Diabetic Dyslipidemia of Drugs Used to Lower Blood Glucose Levels

Several drugs used to treat hyperglycemia can affect plasma lipids and lipoproteins. Metformin has a modest effect on reducing triglycerides and LDL cholesterol [69–71] and has been shown to have some benefit in reducing CVD [72]. How much of these effects are due to the modest weight loss that occurs with its use is uncertain. The GLP1 receptor agonists also can lower triglycerides [73], including postprandial triglycerides [74, 75], although this too may relate to their ability to cause weight loss. Liraglutide also led to a decrease in the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial [76]. These drugs that reduce plasma triglyceride levels also tend to result in a modest increase in HDL cholesterol. Thiazolidinediones (TZDs) decrease triglycerides and increase LDL cholesterol, but not apoB [70, 73]. This is the result of the LDL particles becoming more large and buoyant [77]. Pioglitazone use also was associated with some reduction in CVD outcomes in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial [78] and more recently reduced recurrent strokes in patients with metabolic syndrome [79]. The sodium-glucose cotransporter 2 (SGTL2) inhibitors tend to modestly increase both LDL cholesterol and apoB [80–83], suggesting an increase in the number of LDL particles. These findings need to be put in the context of the widespread use of statins in type 2 diabetes and the metabolic syndrome, and the beneficial effects of which on LDL are likely to override the adverse effects of LDL cholesterol increases that occur with the use of some of these hypoglycemic agents. Moreover, empagliflozin and more recently canagliflozin were associated with a reduction in clinical cardiovascular events and deaths [84•, 85]. Sulfonylureas and dipeptidyl peptidase 4 (DPP4) inhibitors are in general lipid neutral [73, 80] or have mild beneficial effects [70, 86], but have not been shown to affect CVD outcomes [87, 88].

Special Consideration

Multifactorial Chylomicronemia Syndrome

Plasma triglyceride levels sometimes become markedly elevated in patients with diabetes, putting them at risk of triglyceride-induced pancreatitis and other features of the chylomicronemia syndrome [89]. Levels > 1000 mg/dL usually indicate an interaction between genetic forms of hyperlipidemia [90] with secondary causes of hypertriglyceridemia, the most common of which is undiagnosed, untreated, or inadequately treated diabetes [90]. Levels fall in response to treatment of the diabetes by whatever means is indicated, but also require attention to other conditions that can cause secondary hypertriglyceridemia such as hypothyroidism, alcohol, and the use of triglyceride-raising drugs, particularly diuretics and beta-blockers. Triglyceride levels seldom fall to the normal range after treatment; rather, they decline to levels typical of the underlying genetic hyperlipidemia [90]. To prevent recurrence of very high levels, use of fibrates is usually indicated. Many such patients also have strong family

histories of premature CVD and require statin therapy for CVD prevention in addition to strategies to keep their triglycerides under control.

Partial Lipodystrophy

A rare cause of very severe hypertriglyceridemia and insulin resistant diabetes is partial lipodystrophy. The Dunnigan variety is often due to mutations in the lamin A/C gene [91, 92], but no consistent mutations have been found in the more common and often underdiagnosed Kobberling variety. Diagnosis of this disorder is purely on clinical grounds [93]. Patients with partial lipodystrophy have a high incidence of CVD [93, 94]. Moreover, the hypertriglyceridemia and insulin-resistant diabetes seen in such patients are difficult to treat. They often require triglyceride-lowering strategies such as omega-3 fatty acids in addition to fibrates, and in our experience, some respond to GLP-1 receptor agonists and TZDs. Very high doses of insulin, including the use of U500 insulin, may be required to achieve reasonable glycemic control.

Use of Guidelines

Several guidelines are available for the treatment of dyslipidemia in diabetes. The American Diabetes Association (ADA) issues an annual clinical practice guideline, the American Heart Association/American College of Cardiology (AHA/ACC) cholesterol guidelines are widely used for management of people with diabetes in the USA, and guidelines are available from the National Lipid Association (NLA) and National Institute for Health and Care Excellence in the UK, as well as specific guidelines for the management of diabetic dyslipidemia from American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE). While each set of guidelines differs from each other to some extent, there is consistency of recommendation that lifestyle changes and the use of statins are the primary modes of management of diabetic dyslipidemia and CVD prevention in people with diabetes. In addition, measures such as cessation of smoking, blood pressure control, and excellent glycemic control are all part of the management of people with diabetes. The major differences among these guidelines relates to what age lipid-lowering therapy should be initiated and above what age it should not be started, thereby allowing for clinical judgment based on overall CVD risk. There also are differences in recommendations regarding which risk calculator to use.

Perhaps the most controversial issue in the various guidelines relates to lipid-lowering therapy in patients with type 1 diabetes. Type 1 diabetic subjects at greatest risk for CVD events are those with established CVD, nephropathy, hypertension, features of the metabolic syndrome (as seen in those who gained the most weight in the intensively treated arm of the DCCT [95, 96]), and other CVD risk factors including a positive family history [93]. The extent of increased risk in type I diabetic patients without these other issues remains unclear. Nonetheless, most guidelines recommend the use of statins as for type 2 patients, usually recommending starting at the age of 40. Since the onset of type 1 diabetes most often occurs at a much younger age, it might be prudent to start therapy earlier, although no data are available to support this idea.

Remaining Questions and Unmet Needs

While large strides have been made toward preventing cardiovascular complications of diabetes by treating dyslipidemia with statins, a large residual risk remains. Clearly, there is tremendous need to reduce this risk, especially in view of the alarming increase in the incidence and prevalence of diabetes. Several unanswered questions remain pertaining to several aspects of diabetic dyslipidemia, and the answers to several of which may be forthcoming in the next few years.

What Levels of LDL Reduction Are Optimal and Therefore Are Our Goals for Therapy? With respect to LDL lowering, it is likely that we will learn a lot more about the safety and efficacy of PCSK9 inhibitors, including their effect in people with diabetes. It is unclear whether a lower threshold exists below which benefit is lost. To date, no problem has arisen at very low levels of LDL cholesterol achieved, which are similar to those seen with mutations in the apoB gene in hypobetalipoproteinemia. Other methods of inhibiting PCSK9 are likely to become available in the not too distant future. A drug under development that uses a siRNA approach to inhibit PCSK9 markedly lowers LDL when administered twice a year [97]. However, it too has to be injected. A new oral inhibitor of ATP citrate lyase, ETC-1002, which is under development, looks promising [98]. Not only does it lower LDL levels but also its ability to activate AMP kinase suggests that it might have a dual effect in lowering both LDL cholesterol and glucose levels. Indeed, it has been shown to reduce blood glucose excursions in subjects with type 2 diabetes [99]. Both PCSK9 inhibitors and ETC-1002 may be of particular value in people with diabetes who are statin intolerant, since neither the PCSK9 antibodies nor ETC-1002 appears to be associated with the myalgias sometimes seen with statins [100, 101].

Are Reductions in Triglycerides Anti-atherogenic? As noted earlier, despite strong suggestive evidence that fibrates have additional cardiovascular benefits when combined with a statin, we for once and for all need to know whether this approach is beneficial when used in appropriate diabetic patients who have residual hypertriglyceridemia on statins. The study alluded to earlier will hopefully provide the unequivocal answer to this question, although there is no control group with any of the commonly used fibrates. Uncertainty also

remains as to the value of omega-3 fatty acids in hypertriglyceridemic subjects.

Will Therapies That Reduce apoC-III or Newer Targets Prove To Be of Value for Both Pancreatitis and CVD Prevention? Of particular interest will be the role of apoC-III inhibition in treating the hypertriglyceridemia associated with diabetes. One company has developed an antisense oligonucleotide that looks extremely promising [102]. Its major use may turn out to be in patients with severe hypertriglyceridemia, in whom it could be used for pancreatitis prevention [52]. Other approaches to lowering apoC-III might have a more widespread use for hypertriglyceridemia. Individuals with mutations in the gene for Angptl 3 have low levels of triglycerides and cholesterol, as well as low risk for CVD [103]. Therefore, drugs to inhibit this pathway also are in development.

HDL

Will HDL Continue To Be a Therapeutic Target and Will Its Use as a CVD Risk Indicator Change? The future of approaches that target HDL is uncertain. Clearly, better metrics than measurement of HDL cholesterol are required. Such measures are likely to be based on HDL function, or alternate measures of HDL particle concentration, proteomics, or lipidomics. Any new measures will need to reduce clinical events and will need to be sufficiently uncomplicated so as to have universal applicability. Although one trial of a CETP inhibitor is still ongoing, fresh approaches to facilitate reverse cholesterol transport that result in improved clinical outcomes are unlikely to be available in the near future.

Lp(a)

Will Lp(a) Reduction Improve Outcome in Patients Already on LDL-Reducing Therapies and/or Will Reduction of Lp(a) Levels Reduce Aortic Valve Disease? Lp(a) is an important and under-recognized cardiovascular risk factor, which has both atherogenic and thrombogenic effects [104]. It is not routinely measured despite its importance as a CVD risk factor. Moreover, it is increased in patients with nephropathy [105] and may contribute to the markedly increased cardiovascular risk associated with diabetic nephropathy. Its value is further complicated by lack of knowledge as to whether lowering Lp(a) levels per se will have cardiovascular benefit. In part, this is due to the lack of drugs that lower Lp(a) levels sufficiently. Niacin can reduce Lp(a) by about 30%, and PCSK9 inhibitors unexpectedly were found to reduce Lp(a) by a similar magnitude [106]. However, since the distribution of Lp(a) is markedly skewed to the right, these changes rarely bring levels into an acceptable percentile range. Recently, the use of an antisense oligonucleotide against apo(a) has been shown to reduce apo(a) levels by about 90% [107], which should allow a clinical trial to be performed to test the value of specifically lowering Lp(a) levels. If such a trial is positive, Lp(a) lowering might with time be of value in subjects with elevated levels, especially in diabetic nephropathy. Moreover, Lp(a) was recently found to be a genetic marker for risk of aortic stenosis [108]. This had led to the exciting possibility that aortic stenosis could be preventable.

Type 1

Should the Approach to Treatment of Lipid Disorders in Patients With Type 1 Diabetes Differ From Those With Type 2 Diabetes? Finally, much remains to be learned about lipid-lowering therapy in patients with type 1 diabetes. Since their lipid profiles improve markedly following institution of treatment and achieving good glycemic control, the approach to the type 1 patient, who nonetheless has an increased risk of CVD, might with time turn out to be different to the approach used in the type 2 patient. It will be important to recognize the type 1 patient who concurrently has features of the metabolic syndrome, such as the classical dyslipidemic pattern, central obesity, hypertension, and increased inflammatory and thrombotic markers, since the approach to treatment in such type 1 patients may be more akin to individuals with the metabolic syndrome and type 2 diabetes.

Conclusion

While awaiting the outcome of several clinical trials and new approaches to drug treatment of diabetic dyslipidemia, current therapy should focus on the use of statins, which have been shown to reduce CVD associated with diabetic dyslipidemia in both types 1 and 2 diabetes, as well as the metabolic syndrome. These should be undertaken in conjunction with lifestyle measures and excellent glycemic control, the latter of which has been shown to have more pronounced effect in the prevention of microvascular rather than macrovascular complications of diabetes. In the meantime, several exciting new therapeutic advances are likely to provide additional therapeutic approaches to diabetic dyslipidemia and CVD prevention in diabetes in the not too distant future.

Compliance with Ethical Standards

Conflict of Interest Alan Chait reports personal fees from Ionis Pharmaceuticals and Merck.

Ira Goldberg reports personal fees from Ionis Pharmaceuticals, Amgen, Merck, and Sanofi/Regeneron.

Human and Animal Rights and Informed Consent This article contains some studies with human subjects performed by the authors. Informed consent was obtained from all individual participants included in those studies.

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- •• Of major importance

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