

# Diabetic Dyslipidemia and Atherosclerosis

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Atherosclerosis is the primary cause of death in patients with type 2 diabetes mellitus (DM) and it seems to be closely related to a specific cluster of lipid abnormalities, including low levels of high-density lipoprotein cholesterol, increased numbers of small dense low-density lipoprotein particles, and elevated triglyceride levels. Each of these abnormalities is associated with an increased risk for cardiovascular morbidity and mortality. This review describes the atherogenic dyslipidemia that characterizes type 2 DM, the causes of this so-called *diabetic dyslipidemia*, and pharmacologic approaches to normalizing the lipid profile in these patients. The management of patients with type 2 DM usually centers on glycemic and blood pressure control. Most of the commonly used antidiabetic agents have neutral or only mildly beneficial effects on diabetic dyslipidemia; thus, achieving better glycemic control may only slightly improve the lipid profile. Treatment of dyslipidemia usually requires pharmacotherapy to achieve major improvements in lipid profiles, yet current management of diabetic dyslipidemia generally is not optimal. Even when treated with statins, patients with type 2 DM frequently exhibit a residual risk for cardiovascular disease; therefore, additional treatment options that use mechanisms of action that differ from those of statins are needed. New agents such as ezetimibe, along with the more traditional treatments of statins, fibrates, and nicotinic acid, may potentially improve the lipid profiles of patients with diabetic dyslipidemia. (*Clinical Cornerstone*. 2008;9[Suppl 2]:S17–S27) © 2008 Elsevier.

Patients with type 2 diabetes mellitus (DM) have an increased risk for morbidity and mortality from cardiovascular disease (CVD), which typically manifests as coronary artery disease (CAD), peripheral arterial disease, and cerebrovascular disease.<sup>1</sup> Most of the premature morbidity and mortality in these patients is due to CAD, and the risk of CAD in patients with type 2 DM is increased ~2- to 4-fold over that in patients without type 2 DM.<sup>2</sup> The high incidence of CVD in patients with type 2 DM cannot be explained completely by hyperglycemia<sup>1</sup>; furthermore, traditional cardiovascular risk factors, such as hypertension and smoking, can only partly explain the increased risk of CVD.<sup>3</sup> Dyslipidemia, a cluster of lipid abnormalities, including low levels of high-density lipoprotein (HDL) cholesterol (HDL-C), increased numbers of small dense low-density lipoprotein (LDL) particles, and elevated triglyceride levels, is common in patients with type 2 DM, and the presence of these lipid abnormalities may be a more important risk factor for CVD than is

hyperglycemia.<sup>3</sup> This review will describe the atherogenic dyslipidemia that characterizes type 2 DM, often called *diabetic dyslipidemia*; the causes of this dyslipidemia; and pharmacologic approaches to normalizing the lipid profile in these patients.

## DIABETIC DYSLIPIDEMIA

Dyslipidemia has been defined as a total cholesterol, LDL-C, or triglyceride level above the 90th percentile for the general population, or a low HDL-C level.<sup>4</sup> The dyslipidemia that is associated with type 2 DM, however, does not include an increased LDL-C level. In fact, the prevalence of high concentrations of LDL-C in patients with diabetes is similar to that for the general population; however, there is a difference in the distribution of LDL particle sizes, as patients with diabetes have an increased number of small dense LDL particles compared with individuals in the general population.<sup>3</sup> Furthermore, patients with type 2 DM are 2 to 3 times more likely to have

elevated triglyceride levels and reduced HDL-C levels than individuals in the general population.<sup>5</sup> A simplified outline of the metabolic pathway of lipids in patients with diabetes is shown in **Figure 1**.<sup>6</sup>

**KEY POINT**

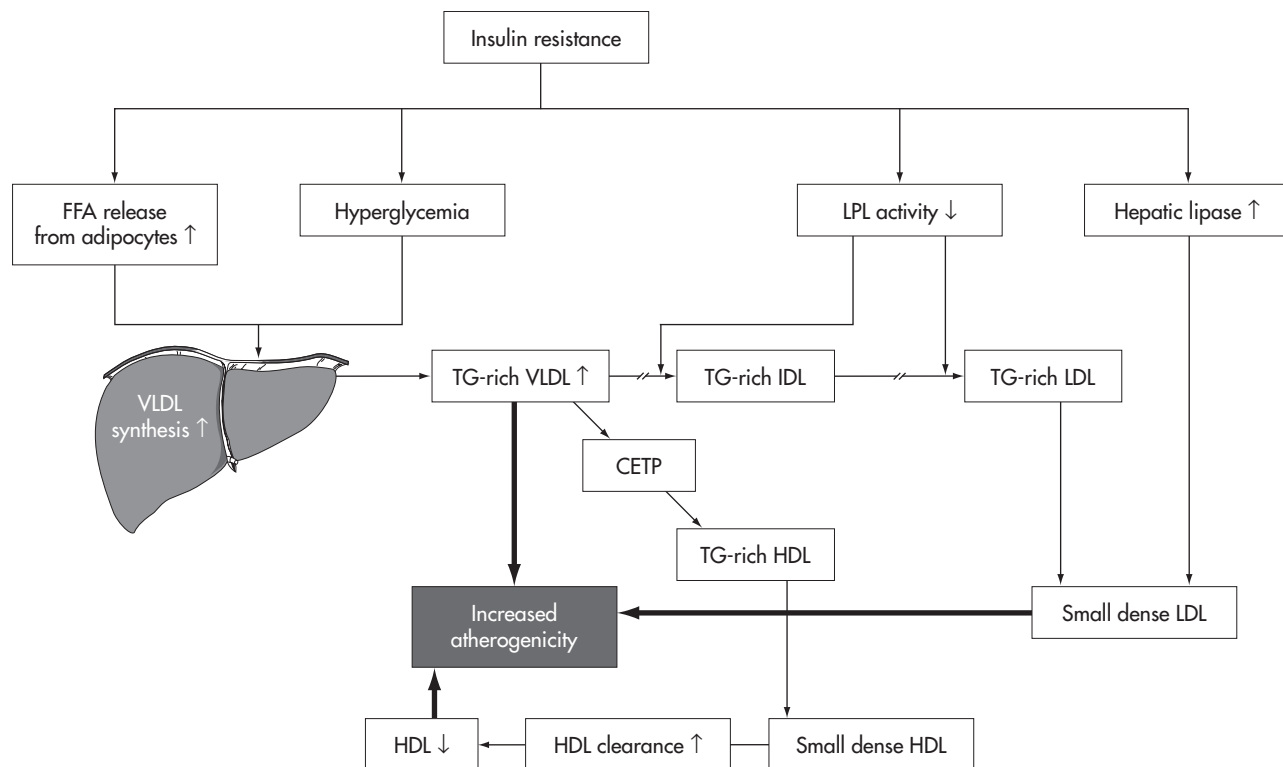
**The prevalence of high concentrations of LDL-C in patients with diabetes is similar to that for the general population; however, patients with diabetes have an increased number of small dense LDL particles.**

Epidemiologic evidence provides support for the hypothesis that these changes in the lipid profile are responsible for the observed increased risk for CVD in patients with type 2 DM. For example, one of the results of the

United Kingdom Prospective Diabetes Study (UKPDS)<sup>7</sup> was to show that an increased concentration of LDL-C is a potentially modifiable risk factor for CAD in patients with type 2 DM. In this study, a 1-mmol/L (39-mg/dL) reduction in LDL-C levels was associated with a 36% reduction in the risk for CVD.

The importance of HDL-C for cardioprotection is illustrated by epidemiologic studies that demonstrate an inverse relationship between HDL-C levels and CVD risk.<sup>3,8</sup> In the Framingham study,<sup>8</sup> CVD risk was increased ~6-fold in women with HDL-C levels <1.2 mmol/L (46 mg/dL) compared with women whose levels were >1.7 mmol/L (66 mg/dL). In the UKPDS,<sup>7</sup> the relative risk of CVD decreased 0.15-fold (0.08–0.22) for each 0.1-mmol/L (3.9-mg/dL) increase in HDL-C levels in patients with type 2 DM. Additional evidence for the protective role of HDL-C is suggested by the observation that plasma concentrations of HDL-C >1.9 mmol/L (73 mg/dL) are associated with prolonged life (ie, longevity syndrome).<sup>9,10</sup>

Hypertriglyceridemia is regarded as an independent risk factor for CAD.<sup>1</sup> In a meta-analysis of



**Figure 1. Simplified metabolic pathway of lipids in patients with insulin resistance/diabetes. FFA = free fatty acid; ↑ = increased; LPL = lipoprotein lipase; ↓ = decreased; VLDL = very-low-density lipoprotein; TG = triglyceride; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; CETP = cholesteryl ester transfer protein; HDL = high-density lipoprotein. Adapted with permission.<sup>6</sup>**

6 large prospective studies,<sup>11</sup> strong associations were observed between triglyceride levels measured in the fasting state and CAD, with a 76% increase in risk for women and a 32% increase in risk for men for every 1-mmol/L (88.5-mg/dL) increase in triglyceride levels.

### Low-Density Lipoprotein Cholesterol

The major physiologic role of LDL-C is to provide cholesterol for use in the repair of cellular membranes and for the synthesis of steroid hormones and vitamin D.<sup>1</sup> Patients with type 2 DM usually exhibit normal levels of plasma LDL-C; however, significant changes in the metabolism of LDL-C occur (Table I, Figure 1).<sup>5,6</sup> Specifically, the catabolism rate of LDL particles is reduced (possibly because of a reduction of the number of LDL receptors), as is the rate of LDL-C production.<sup>5</sup> These changes result in a reduced turnover of LDL particles, along with an increased LDL-C plasma residence time that may promote cholesterol deposition in the arterial wall. Furthermore, the hypertriglyceridemia that occurs in patients with type 2 DM may be responsible for the change in the size distribution of LDL particles. The increase in the levels of triglyceride-rich lipoproteins stimulates cholesteryl ester transfer protein (CETP) activity, which promotes the transfer of triglycerides to LDL particles, resulting in the formation of triglyceride-rich LDL particles. The hepatic lipase enzyme, which is more active in patients with type 2 DM, converts triglyceride-rich LDL particles into small dense LDL particles.<sup>5</sup>

### KEY POINT

**The hypertriglyceridemia that occurs in patients with type 2 DM may be responsible for the change in the size distribution of LDL particles.**

### High-Density Lipoprotein Cholesterol

The decrease in HDL-C levels typically observed in patients with type 2 DM is due to the increased catabolism rate of HDL particles (Table I).<sup>5</sup> The hypertriglyceridemia that occurs in patients with type 2 DM results in an increased pool of triglyceride-rich lipoproteins, mainly very-low-density lipoproteins (VLDL), that drives the transfer of triglycerides from triglyceride-rich lipoproteins to HDL particles via the enzyme CETP. Lipid-enriched HDL particles are more rapidly catabolized, resulting in the reduced plasma levels of HDL-C that is common in this patient population.<sup>1</sup> Triglyceride-rich HDL particles are a good substrate for hepatic lipase, the activity of which results in smaller HDL particles.<sup>5</sup>

### Triglycerides

The increase in plasma triglyceride levels observed in patients with type 2 DM is mainly due to an increase in the number of VLDL particles.<sup>5</sup> There is also a reduction in the catabolism rate of VLDL particles as a result of the reduced activity of lipoprotein lipase. Lipoprotein lipase

**TABLE I. LIPID ABNORMALITIES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS.**

Lipid Abnormality	Kinetic Abnormality	Qualitative Abnormality
↑ VLDL (hypertriglyceridemia)	↑ Production	Large VLDL (VLDL1)
	↓ Catabolism	Glycation*
↑ LDL (normal or slightly elevated)	↓ Catabolism	Small dense LDL (TG-rich LDL)
	↓ Turnover	Oxidation
↓ HDL	↑ Catabolism	Glycation*
		TG-rich HDL
		Glycation*

↑ = increase; VLDL = very-low-density lipoprotein; ↓ = decrease; LDL = low-density lipoprotein; TG = triglyceride; HDL = high-density lipoprotein.  
\*Glycation is a nonenzymatic reaction between a sugar and a free amino group of proteins.  
Adapted with permission.<sup>5</sup>

degrades the triglycerides within the VLDL particle. Qualitative abnormalities in the size distribution of VLDL particles have also been observed in patients with type 2 DM—specifically, there are increased numbers of large triglyceride- and cholesterol-enriched VLDL particles (VLDL1). Increased levels of free fatty acids can result in insulin resistance in muscle and liver tissue.<sup>12</sup> Furthermore, resulting lipotoxicity can impair pancreatic  $\beta$ -cell function in patients with type 2 DM.

### KEY POINT

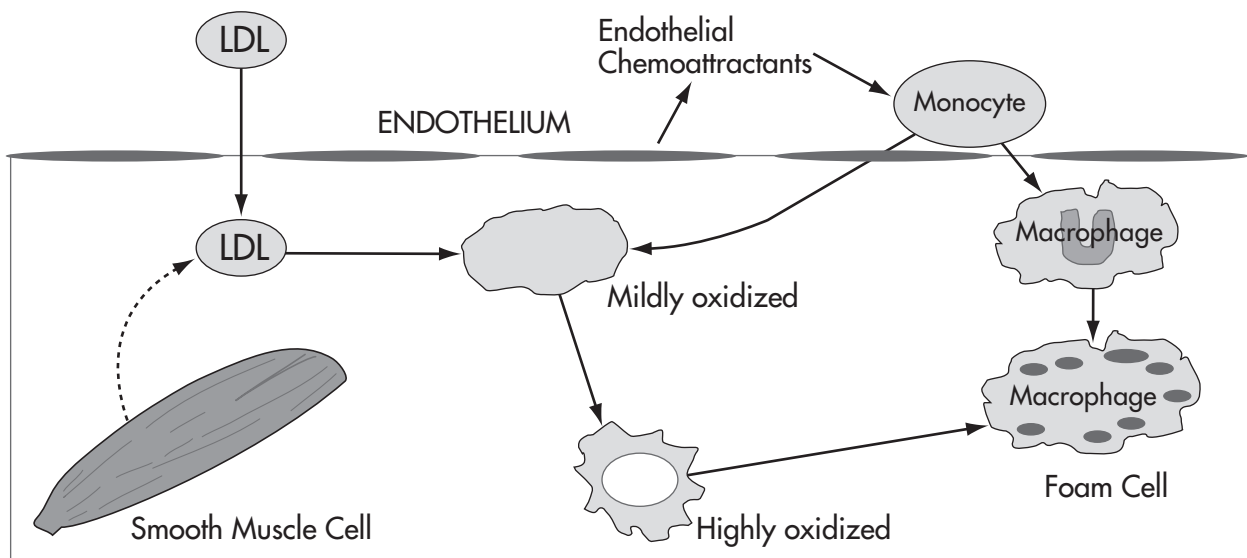
**The increase in plasma triglyceride levels observed in patients with type 2 DM is mainly due to an increase in the number of VLDL particles.**

### DIABETES AND ATHEROSCLEROSIS

Each of the lipid abnormalities that occurs in patients with type 2 DM is a major predisposing factor to the development of atherosclerosis. The small dense LDL particles associated with diabetes possess more atherogenicity than do larger LDL particles.<sup>13</sup> Characteristics that

may play a role in the increased atherogenicity of small dense LDL particles include: (1) reduced LDL receptor affinity, (2) increased binding to arterial wall proteoglycans, and (3) increased susceptibility to oxidation.<sup>14</sup> For example, small dense LDL particles penetrate the endothelial barrier 1.7 times more easily than do larger LDL particles, and they remain longer in the subendothelial matrix (Figure 2).<sup>13,15,16</sup> Small dense LDL particles are more readily oxidized or otherwise modified, and modified LDL particles play an important role in atherogenesis.<sup>13</sup> Oxidative modification of LDL particles results in rapid uptake by macrophages, with subsequent formation of foam cells.<sup>14</sup> LDL particles can promote inflammatory and immune changes via cytokine release from macrophages. Foam cells can rupture, releasing oxidized LDL particles, intracellular enzymes, and oxygen-free radicals that can further damage the vessel wall. Oxidized LDL particles can produce the following additional atherogenic effects<sup>17–25</sup>: (1) apoptosis of vascular smooth muscle and endothelial cells, (2) disruption of the endothelial cell surface and further impairment of endothelial function, (3) an increase in platelet aggregation that contributes to vascular thrombus formation, and (4) plaque instability.

An additional proatherosclerotic mechanism in type 2 DM is the increased synthesis of large VLDL1 particles.<sup>5</sup> VLDL1 particles are taken up by receptors located on



**Figure 2.** In vitro studies suggest that small dense low-density lipoprotein (LDL) particles slip through the endothelial barrier more easily than do large buoyant LDL particles. The smaller particles remain longer in the subendothelial matrix, and they are more readily oxidized or otherwise modified than are the larger LDL particles. Adapted with permission.<sup>13</sup>

**KEY POINT**

**Small dense LDL particles are more readily oxidized or otherwise modified, and modified LDL particles play an important role in atherogenesis.**

macrophages, thus promoting the accumulation of lipids within macrophages and contributing to the formation of foam cells in vessel walls. Furthermore, hypertriglyceridemia is associated with prothrombotic and inflammatory changes that may contribute to the increased risk of CVD observed in patients with type 2 DM.<sup>1</sup>

A major factor contributing to the antiatherogenic properties of HDL-C is thought to be reverse cholesterol transport, a process by which excess amounts of cholesterol located in cells and atherosclerotic plaques are removed.<sup>26</sup> The net effect of this process is the observed inverse relationship between plasma HDL-C levels and cardiovascular risk.<sup>9,27</sup> Other functions of HDL-C that contribute to antiatherogenicity are the maintenance of endothelial function<sup>28,29</sup> and improvement in fibrinolytic balance.<sup>30–33</sup>

**TREATMENT OF DYSLIPIDEMIA**

Treatment of dyslipidemia usually requires pharmacotherapy to achieve major improvement in lipid profiles<sup>1</sup>; however, management of patients with type 2 DM usually centers on glycemic and blood pressure control. Many of the commonly used antidiabetic agents have either neutral specific effects (eg, sulfonylureas, meglitinides) or only mildly beneficial effects (eg,  $\alpha$ -glucosidase inhibitors) on the dyslipidemia associated with type 2 DM.<sup>3</sup> However, improving glycemic control with insulin can improve triglyceride levels. Pioglitazone and metformin also have been shown to reduce plasma levels of triglycerides.

**KEY POINT**

**Improving glycemic control with insulin can also improve triglyceride levels.**

**Statins**

Statins—atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin—are the major class of agents used to treat hypercholesterolemia. The statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting step in cholesterol biosynthesis. This inhibition results in the following sequence of events<sup>5</sup>: inhibition of cholesterol synthesis, an increase in the number of surface LDL receptors, an increase in the rate of LDL-C clearance from plasma, and, ultimately, a lowering of circulating LDL-C levels. In addition to being very effective at lowering LDL-C levels in patients with type 2 DM, statins can also produce a moderate reduction in triglyceride levels and a minor increase in HDL-C levels. Because patients with type 2 DM have a high absolute risk of CVD, those treated with statins may have a greater reduction in risk than do individuals in the general population. In the Scandinavian Simvastatin Survival Study,<sup>34</sup> there was a 43% reduction in total mortality risk versus a 29% reduction and a 55% reduction in risk for myocardial infarction (MI) versus a 32% reduction, respectively, among patients with and without diabetes.

The Collaborative Atorvastatin Diabetes Study (CARDS)<sup>35</sup> was the first clinical trial designed specifically to test the efficacy of a statin in a population of patients with type 2 DM. Diabetic patients without a history of CVD but with at least one other risk factor (retinopathy, albuminuria, current smoker, or hypertension) were randomized to receive either atorvastatin (10 mg/d) or placebo and were followed for a median of 3.9 years. There was a reduction of 37% in the incidence of major cardiovascular events in the atorvastatin group ( $P = 0.001$  vs placebo), although a reduction of 27% in total mortality in this group did not reach statistical significance ( $P = 0.059$  vs placebo).

Currently, management of diabetic dyslipidemia is generally not optimal. Even when treated with statins, patients with type 2 DM frequently exhibit a residual risk for CVD,<sup>5</sup> as most statins, when prescribed at low doses, have only modest effects on HDL-C and triglyceride levels.<sup>3</sup> However, some of the newer, more potent statins (eg, rosuvastatin) are very effective in lowering triglyceride levels.<sup>36</sup> Nevertheless, additional pharmacotherapeutic options with mechanisms of actions that are complementary to those of statins are also needed.

**KEY POINT**

**Management of diabetic dyslipidemia is generally not optimal. Even when treated with statins, patients with type 2 DM frequently exhibit a residual risk for CVD.**

### **Peroxisome Proliferator-Activated Receptor Agonists**

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that belong to the superfamily of nuclear receptors. Three isoforms, encoded by separate genes, have been identified—PPAR- $\alpha$ , PPAR- $\gamma$ , and PPAR- $\delta$ . These isoforms share 60% to 80% homology. Although PPAR- $\alpha$  and PPAR- $\gamma$  are predominantly expressed in liver and adipose tissue, respectively, PPAR- $\delta$  is present in many tissues of the body.<sup>37</sup> Agonists specific for the different PPAR isoforms have been developed and are either in clinical use or in clinical trials.

### **Fibrates**

The fibrates—gemfibrozil and fenofibrate, as well as bezafibrate and clofibrate, which are not currently available in the United States—are specific ligands for PPAR- $\alpha$ . These agents have beneficial effects on all 3 aspects of diabetic dyslipidemia: they reduce levels of small dense LDL particles and triglycerides, and they raise levels of HDL-C. These effects are achieved as a consequence of the following mechanisms of action<sup>5</sup>: (1) induction of lipoprotein lipolysis and hepatic fatty acid uptake, (2) reduction of hepatic triglyceride production, (3) increase in the removal of LDL particles and the production of HDL-C, and (4) stimulation of reverse cholesterol transport.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study<sup>38</sup> was the largest placebo-controlled clinical outcomes study of a lipid-modifying medication in a population of patients with type 2 DM, and the first cardiovascular outcomes trial for fenofibrate treatment. In the FIELD study, 9795 patients with type 2 DM (many of whom also had metabolic syndrome) were randomized to receive either fenofibrate (200 mg) or

placebo. The primary end point was a reduction in risk for coronary events (nonfatal MI or coronary death) over 5 years. Treatment with fenofibrate did not significantly reduce the risk for coronary events, as results of the study showed a reduction in nonfatal MI (24%;  $P = 0.01$ ) but an increase in coronary heart disease mortality ( $P = 0.22$ ); however, it did reduce the incidence of total coronary events (13.9%–12.5%;  $P = 0.035$ ), mainly because of the reduction in nonfatal MI.

### **Thiazolidinediones**

Thiazolidinediones (TZDs) are PPAR- $\gamma$  ligands that have positive effects on glucose homeostasis, lipid metabolism, and the progression of atherosclerosis. There are 2 TZDs currently available—pioglitazone and rosiglitazone. The specific effects of TZDs on diabetic dyslipidemia include an increase in plasma HDL-C levels, a reduction in the number of small dense LDL particles, and an increase in the proportion of large, buoyant LDL particles.<sup>5</sup> In a summary analysis of 19 double-blind, placebo-controlled trials,<sup>39</sup> pioglitazone was associated with more beneficial lipid effects than was rosiglitazone. Treatment with pioglitazone produced significant reductions in triglyceride levels and was associated with a greater increase in HDL-C levels than was treatment with rosiglitazone.

### **Dual PPAR- $\alpha$ /PPAR- $\gamma$ Agonists**

Because PPAR- $\alpha$  and PPAR- $\gamma$  exert their beneficial effects on diabetic dyslipidemia through different mechanisms of actions (PPAR- $\alpha$  increases lipid catabolism, whereas PPAR- $\gamma$  increases fat storage and improves insulin sensitivity), one might expect activation of both receptors to show synergistic improvements in the lipid profile. However, because of potential drug–drug interactions that could increase the frequency of side effects, the combination of a selective PPAR- $\alpha$  agonist and a selective PPAR- $\gamma$  agonist may not be the optimal approach.<sup>3</sup> A different approach, combining the selective activation of the 2 PPAR isoforms into 1 molecule, a dual PPAR- $\alpha$ /PPAR- $\gamma$  agonist, has produced 2 drugs that are in late clinical development—muraglitazar and tesaglitazar. However, results from recent clinical studies of these agents raise questions about the safety of the dual PPAR- $\alpha$ /PPAR- $\gamma$  agonist class. The clinical development of tesaglitazar was terminated because of emerging safety data suggesting that the overall benefit to risk pro-

file for the drug was unlikely to be superior to currently available therapies.<sup>12</sup> The continued development of muraglitazar was called into question when an analysis of Phase II and III clinical trials showed that treatment with muraglitazar was associated with a greater occurrence of death, major cardiovascular events, and congestive heart failure than was placebo or glucose-lowering agents.<sup>40</sup> Thus, although the concept of a dual PPAR- $\alpha$ /PPAR- $\gamma$  agonist is attractive, experience to date indicates that there are obstacles that need to be overcome before these agents can be considered for use in clinical practice.

### Nicotinic Acid

Nicotinic acid (niacin) is a B complex vitamin that reduces plasma concentrations of triglycerides, total cholesterol, and LDL-C, and increases concentrations of HDL-C.<sup>14</sup> Treatment with nicotinic acid also reduces the number of small dense LDL particles. The Coronary Drug Project<sup>41</sup> studied the effect of nicotinic acid (1–3 g/d) as monotherapy on the rate of cardiovascular events in patients with prior MI. The risk of recurrent nonfatal MI was reduced by 27%. A recent subanalysis of this study<sup>42</sup> showed the same results in patients with fasting hyperglycemia (blood glucose >126 mg/dL). However, most often, niacin is not used as monotherapy but as combination therapy with other drugs, usually a statin. Furthermore, doses >2 g/d have been associated with increased insulin resistance and deterioration of glycemic control.

### Combination Therapy

Because of the residual risk for CVD observed in patients with type 2 DM, even when treated with statins, combinations of different lipid-lowering drugs are frequently used. **Table II** lists some of the advantages and disadvantages of combination therapy for the treatment of diabetic dyslipidemia.<sup>43</sup>

### Statins and Niacin

In the HDL Atherosclerosis Treatment Study,<sup>44</sup> the combination of simvastatin and niacin was studied in 160 patients with established coronary heart disease and low HDL-C levels (<0.9 mmol/L [35 mg/dL] in men and <1.03 mmol/L [40 mg/dL] in women), 34 of whom had diabetes or impaired fasting glucose. Combination therapy decreased triglyceride levels by 40% and LDL-C levels by 31% and increased HDL-C levels by 30%. Combination therapy was associated with less progression of average coronary stenosis and a trend toward fewer clinical events. Glycemic control did not deteriorate with this treatment.

### Statins and Fibrates

Adding a fibrate to statin therapy can potentially further increase HDL-C levels and lower triglyceride levels; however, this combination may be associated with an increased risk for side effects (eg, myopathy, abnormal liver function tests).<sup>3</sup> The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, sponsored by the

**TABLE II. ADVANTAGES AND DISADVANTAGES OF COMBINATION THERAPY FOR DIABETIC DYSLIPIDEMIA.**

Advantages	Disadvantages
Further decrease in LDL-C levels	Increase in myopathy; greater with fibrates than with niacin
Decrease in triglyceride levels; increase in HDL-C levels	Drug interactions; adverse reactions (liver; increase in uric acid levels with niacin)
Decrease in lipoprotein (a) levels with niacin	Costs
Decrease in apolipoprotein B and non-HDL-C levels	Lack of evidence-based outcome studies
More patients at ADA and NCEP goals	Increased blood glucose with niacin doses >2 g
Decrease in number of small LDL particles	Short-term increase in insulin levels with niacin
Emerging studies with niacin/statin	
Possible greater risk reduction than can be achieved with LDL-C lowering	

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; ADA = American Diabetes Association; NCEP = National Cholesterol Education Program. Adapted with permission.<sup>43</sup>

National Institutes of Health/National Heart, Lung, and Blood Institute, is expected to be completed in 2009 and will provide information on the relative effects of statin therapy alone and in combination with fibrates.<sup>45–47</sup> The ACCORD trial, which has a double 2 × 2 factorial design, has enrolled >10,000 patients to study the effects of intensive glycemic and blood pressure control in patients with diabetes. In one arm of the study, >5500 patients have been randomized to either a statin alone or a statin in combination with a fibrate to assess the effects of further HDL-C and triglyceride level modification in addition to LDL-C-lowering therapy.

### Statins and Ezetimibe

Ezetimibe, a selective cholesterol absorption inhibitor, lowers cholesterol levels by inhibiting the absorption of both dietary and biliary cholesterol at the brush border of the small intestine.<sup>3</sup> Ezetimibe monotherapy has been shown to reduce serum LDL-C and triglyceride levels (17%–18% and 2%–6%, respectively) and to increase HDL-C levels (1%–2%).<sup>48</sup> Ezetimibe in combination with low-dose atorvastatin (10 mg/d) resulted in reductions in LDL-C levels that were similar to those seen with atorvastatin (80 mg/d) as monotherapy.<sup>49</sup> Thus, combination therapy with ezetimibe may reduce the need for high dosages of statins to achieve required lipid goals. Ezetimibe monotherapy is also useful in patients who cannot tolerate treatment with statins.

### Cholesteryl Ester Transfer Protein Inhibitors

Because increased levels of CETP appear to be associated with atherosclerosis in patients with type 2 DM, a new approach to the treatment of diabetic dyslipidemia is inhibition of CETP.<sup>5</sup> Torcetrapib, an example of this class of drug, has been investigated. However, a Phase III clinical trial was terminated when an increased rate of mortality was observed in the torcetrapib treatment group relative to that in the placebo group.<sup>50</sup> Furthermore, imaging studies have shown that treatment with torcetrapib had no effect on the progression of atherosclerosis, as measured by changes in the percent coronary atheroma volume.<sup>51</sup> Final results of the torcetrapib clinical trial were recently published.<sup>52</sup> Despite the very favorable lipid changes in the torcetrapib group (HDL-C levels increased by 72.1% and LDL-C levels decreased by 24.9%), the rate of major cardiovascular events was increased by 25% and that of death from cardiovascular

causes by 40%. Furthermore, death from noncardiovascular causes was increased 2-fold. These results suggest that simply increasing HDL-C levels may not be sufficient to produce an overall beneficial outcome.

### Cannabinoid-1 Receptor Blockers

The endocannabinoid system (ECS) modulates energy homeostasis and glucose and lipid metabolism through effects on the central nervous system, as well as peripheral metabolic effects in adipose tissue, liver, and skeletal muscle.<sup>53,54</sup> It was thought that blockade of ECS receptors—the CB<sub>1</sub> receptors—therefore, might be advantageous for the prevention of atherosclerosis or for the treatment of dyslipidemia.<sup>55</sup> Treatment with rimonabant, a CB<sub>1</sub> receptor agonist, was shown to produce clinically significant changes in cardiovascular risk factors associated with diabetic dyslipidemia. In the Rimonabant in Obesity (RIO)–Diabetes trial,<sup>56</sup> 1047 overweight or obese patients with type 2 DM inadequately controlled with metformin or a sulfonylurea received either rimonabant (20 mg/d) or placebo. HDL-C, triglyceride, and non-HDL-C concentrations were found to have improved more with rimonabant than with placebo ( $P < 0.01$  for all comparisons). After adjusting for weight loss, treatment with rimonabant produced a 57% residual effect on HDL-C levels ( $P < 0.01$ ). The residual effect on triglyceride levels after adjustment for weight loss was 36%. The improvement in HDL-C levels was twice that expected from weight loss alone, consistent with the direct peripheral metabolic effects of the drug. The results of this study suggested that, in addition to improving glycemic control, treatment with rimonabant may also reduce various cardiovascular and metabolic risk factors in overweight or obese patients with type 2 DM. There is, however, an increased risk for psychiatric adverse events in patients treated with this agent.<sup>57</sup>

In a 12-week weight-loss study,<sup>58</sup> treatment with taranabant, an acyclic CB<sub>1</sub> receptor inverse agonist, in doses of 0.5, 2, 4, and 6 mg resulted in a dose-dependent least squares mean weight loss of 2.8, 3.7, 4.2, and 5.3 kg ( $P < 0.01$ ), respectively, versus placebo (1.3 kg), as well as a dose-response trend in change in waist circumference of –4.4, –4.4, –4.7, and –5.1 cm versus placebo (–2.8 cm). There were no significant changes in glycemic or lipid measures over the range of doses, nor were there any significant effects on systolic or diastolic blood pressure. Treatment with taranabant resulted in a dose-related

increase in gastrointestinal and psychiatric adverse events; therefore, development of this agent has been discontinued.<sup>57</sup>

## CONCLUSIONS

Atherosclerosis, the main cause of death in patients with type 2 DM, seems to be closely related to diabetic dyslipidemia. Each of the abnormalities that comprise diabetic dyslipidemia (low HDL-C levels, increased numbers of small dense LDL particles, and elevated triglyceride levels) is associated with an increased risk for cardiovascular morbidity and mortality. Lowering LDL-C levels is usually the first treatment target in patients with type 2 DM, but abnormalities in HDL-C and triglyceride levels also should be treated aggressively. The traditional treatment options, including statins, fibrates, and nicotinic acid, along with new agents such as ezetimibe, may potentially improve the lipid profiles of patients with diabetic dyslipidemia.

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