Management of Diabetic Dyslipidemia

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Cardiovascular disease (CVD) is a major cause of morbidity and mortality among subjects who have diabetes. It is estimated that cardiovascular complications are responsible for up to 75% of deaths among people who have type 2 diabetes [1] and constitute up to a twofold to fourfold increased risk of coronary heart disease (CHD), stroke, and peripheral vascular disease events when compared with nondiabetic individuals [2–5]; this risk is considered equivalent to that in nondiabetic subjects who have CHD [6–9]. CVD also is the leading cause of death in subjects who have type 1 diabetes. Moreover, subjects who have diabetes have a worse prognosis than their nondiabetic counterparts after an acute coronary event with a greater frequency of congestive heart failure and an increased fatality rate [10,11]. The increased CHD risk in type 2 diabetes seems to result, at least in part, from a greater burden of established cardiovascular risk factors (eg, elevated blood pressure, obesity, dyslipidemia) [12]. These factors are associated with insulin resistance and emerge early in the evolution of the diabetic state. Thus, prompt identification and management of dyslipidemia in type 2 diabetes has become a cornerstone of diabetes care. The high risk for CVD, coupled with the recognition that large numbers of diabetic subjects do not survive their first event and that their prognosis is much poorer if they do compared with nondiabetic subjects, places a responsibility on physicians to adopt a proactive approach in their therapeutic decision-making for dyslipidemia, despite incomplete clinical trial evidence.

Features of diabetic dyslipidemia

Typically, diabetic dyslipidemia is characterized by a modest elevation in triglyceride levels, reduced high-density lipoprotein cholesterol (HDL-C)
values—and although low-density lipoprotein cholesterol (LDL-C) levels generally are similar to those found in the general population—there is an increased frequency of small, dense low-density lipoprotein (LDL) particles (Table 1). National surveys indicate that 30% to 40% of patients who have diabetes have triglyceride levels that are greater than 200 mg/dL and 10% have levels that are greater than 400 mg/dL [13,14]. In the United Kingdom Prospective Diabetes Study (UKPDS), baseline HDL-C levels were 9% lower in men and 23% lower in women who had diabetes compared with controls [15]. Despite the high frequency of modestly elevated baseline triglyceride levels in the UKPDS (mean baseline 159 mg/dL), a multi-variate analysis found that triglyceride levels did not predict CHD events. LDL-C was the strongest independent predictor of CHD, followed by HDL-C [16]. In the recently reported European Diabetes Prospective Complications Study in 1864 subjects who had type 1 diabetes, lipid parameters did not predict CHD; however, age, waist-to-hip ratio, and albumin excretion rate were positive predictors of CHD [17]. Other abnormalities that were associated with diabetic dyslipidemia include increased triglyceride-rich lipoproteins in the postprandial state (postprandial lipemia), increased remnant lipoproteins, increased apolipoprotein B 100 (apo B) concentration, and an increase in small dense HDL particles [18–20], all of which have been associated with an increased risk for CHD.

### Pathogenesis of diabetic dyslipidemia

An increased flux of free fatty acids to the liver that is associated with insulin resistance and abdominal obesity has been implicated in the enhanced production of large very low density lipoprotein (VLDL) particles by the liver [21], the secretion of which is not suppressed by meal-related insulin surges as it normally is in the insulin sensitive state [22]. In addition to VLDL overproduction, reduced lipoprotein lipase activity and apolipo-

<table>
<thead>
<tr>
<th>Plasma lipids</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 2</td>
<td>Control</td>
</tr>
<tr>
<td>No. of patients</td>
<td>2139</td>
<td>52</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>213</td>
<td>205</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>139</td>
<td>132</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>39*</td>
<td>43</td>
</tr>
<tr>
<td>TGs (mg/dL)</td>
<td>159**</td>
<td>103</td>
</tr>
</tbody>
</table>

* Abbreviations: TC, total cholesterol; TGs, triglycerides.
* P < 0.02 comparing type 2 vs. control; **P < 0.001.

protein C III enrichment of VLDL may retard VLDL and remnant clearance [23]. The accumulation of triglyceride-rich lipoproteins, coupled with the heightened action of cholesteryl ester transfer protein, leads to an increased exchange of triglyceride for cholesterol between VLDL and HDL and between VLDL and LDL particles. Hydrolysis of triglyceride-enriched LDL and HDL by hepatic lipase, also considered to be up-regulated in type 2 diabetes, results in the formation of small, cholesterol-poor HDL and LDL particles [24]. There is evidence that diabetic HDL is cleared more rapidly from the circulation and may be dysfunctional [24]. The small, dense LDL pattern (phenotype B) becomes common as triglyceride levels increase to greater than 132 mg/dL [25]. This is twice as frequent in diabetic individuals [20] and is considered to be atherogenic because of an increased vulnerability to oxidative modification and increased uptake by the arterial wall, effects that are aggravated by diabetes [26]. Accumulating exogenous and endogenous remnant lipoproteins are believed to be atherogenic as well [27]. Many of these abnormalities are not reflected directly in the standard lipid profile; this has given rise to several advanced lipoprotein testing methods that can identify lipoprotein size or density subfractions and particle number. The added value that these measurements have in predicting or preventing CVD in high-risk individuals who receive intensive management based on the lipid profile is unclear. They do indicate, however, that the total number of atherogenic particles is increased in type 2 diabetes.

**Benefits of treatment of diabetic dyslipidemia: clinical trial evidence**

Most of the available data that indicate benefit of treatment of dyslipidemia derive from subgroup analyses of intervention trials using statins and suggest that the relative cardiovascular benefits of such treatment are similar among diabetic and nondiabetic participants. Fewer studies used fibrates or niacin. All of these studies confirm the higher risk of CVD events in diabetic subjects.

**Statins**

*Scandinavian Simvastatin Survival Study, Cholesterol and Recurrent Events Trial, and Long-Term Intervention with Pravastatin in Ischemic Disease*

The first three major statin trials, namely the Scandinavian Simvastatin Survival Study (4S; simvastatin, 20–40 mg), the Cholesterol and Recurrent Events Trial (CARE; pravastatin 40 mg) and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID; pravastatin 40 mg), all of which were secondary intervention studies that used different CVD end points and studied subjects with differing mean baseline LDL-C levels (136–185 mg/dL), contained small subgroups of diabetic subjects who
benefited from statin treatment [28–32]. Statin therapy reduced the event rate by an average of 21% to 55% in the diabetic subgroups, although for CARE and LIPID the absolute event rate while on statin therapy remained higher than that in the nondiabetic groups who took placebo. Untested in these trials were the benefits of statin treatment in diabetic subjects who did not have overt CVD, who nevertheless have been placed in the highest risk category by the National Cholesterol Education Panel Adult Treatment Panel (NCEP ATP) III guidelines [9]. Several completed primary prevention trials did not have sufficient power or achieve sufficient LDL-C reduction to produce significant results [33–36]. The question as to whether diabetic subjects without overt heart disease benefit from statin treatment finally was resolved by the Heart Protection Study (HPS) and by the Collaborative Atorvastatin Diabetes Study (CARDS).

Heart Protection Study and Collaborative Atorvastatin Diabetes Study

HPS investigators recruited 5963 diabetic individuals with average cholesterol values (baseline LDL-C 127 mg/dL)—2912 of whom had no clinical features of CVD—and 14,573 nondiabetic individuals who had occlusive vascular disease to test the efficacy of 40 mg of simvastatin compared with placebo [37]. Treatment with simvastatin yielded an approximate 30% reduction in LDL-C and reduced the risk of the first major cardiovascular event by 33% in the diabetic subjects who did not have CVD and by 18% in those who had pre-existing CVD (no significant difference in effect size in these two groups, although placebo and statin-treated groups in those who had pre-existing CHD had major vascular event rates that were more than three times greater than those who did not have pre-existing CHD). These effects were independent of age (all subjects were > 40 years of age), gender, diabetes duration, type of diabetes (there were 600 subjects who had features of type 1 diabetes and who responded in a similar manner to the rest of the group), level of glycemic control, triglyceride, and HDL-C levels. Furthermore, the relative benefit of statin therapy in diabetic individuals whose baseline LDL-C was less than 116 mg/dL at entry was similar to that obtained in those whose LDL-C was greater than 116 mg/dL (27% versus 20% relative risk reduction [RRR] in first major CVD event) (Table 2). (It has been pointed out that because a direct LDL-C method was used in HPS, this LDL-C cut point would be ~120 mg/dL using the standard Friedewald calculation.) There was a sufficient number of individuals among the combined diabetic and nondiabetic cohorts whose baseline LDL-C was less than 100 mg/dL to show that the proportional reduction in CVD event risk by simvastatin was similar to those whose LDL-C was greater than 130 mg/dL [38]. The investigators concluded that “statin therapy should be considered routinely for diabetic patients at sufficiently high risk of major vascular events, irrespective of their initial cholesterol levels” [37]. Most would agree that almost all diabetic subjects who are older than 40 years fit this description.
The CARDS provides strong support for the results in the cohort that had diabetes but no CVD in the HPS [39]. This was the first statin trial to be conducted exclusively in diabetic subjects. The investigators randomized 2838 men and women (mean age 62 years; mean LDL-C, 118 mg/dL) who had type 2 diabetes, but no CVD, and at least one risk factor (hypertension, smoking, micro- or macro-albuminuria, retinopathy) to treatment with placebo or atorvastatin, 10 mg per day. When the study was ended prematurely after a median follow-up of 3.9 years because of the early positive findings, mean LDL-C in the group that received active treatment had decreased to 78 mg/dL and was associated with significant reductions in acute CHD events (36%) and stroke (48%). In similar fashion to the HPS findings, there was a similar relative statin benefit for CHD in subjects who had LDL-C levels that were greater or less than 120 mg/dL.

Reversal of Atherosclerosis and Aggressive Lipid Lowering and Pravastatin or Atorvastatin Evaluation and Infection Therapy Trials

The Reversal of Atherosclerosis and Aggressive Lipid Lowering (REVERSAL) and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trials, reported recently, are the first of a new generation of statin trials that compared the benefits of “moderate” and “intensive” statin therapy. Although neither trial was directed primarily at diabetic subjects, their findings are important for all high-risk patients, and together with HPS led to a reshaping of NECP ATP III. In REVERSAL, 634 subjects who had an identified coronary artery stenotic lesion had the plaque in this area characterized by intravascular ultrasound before and 18 months after randomization to pravastatin, 40 mg per day, or atorvastatin, 80 mg per day [40]. Despite the fact that subjects in the group that received pravastatin achieved a mean LDL-C of 110 mg/dL, plaque volume continued to expand (+2.7%) compared with those in the group that

### Table 2
Heart Protection Study: diabetes subgroup data

<table>
<thead>
<tr>
<th>Measure difference (mg/dL)</th>
<th>CVD event-rate (%/4.8 y)</th>
<th>Placebo</th>
<th>Simvastatin</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C &lt; 116</td>
<td></td>
<td>20.9</td>
<td>15.7</td>
<td>27</td>
</tr>
<tr>
<td>LDL-C ≥ 116</td>
<td></td>
<td>27.0</td>
<td>23.3</td>
<td>20</td>
</tr>
<tr>
<td>HDL-C &lt; 35</td>
<td></td>
<td>31.1</td>
<td>25.9</td>
<td>20</td>
</tr>
<tr>
<td>HDL-C ≥ 35</td>
<td></td>
<td>21.3</td>
<td>15.8</td>
<td>27</td>
</tr>
<tr>
<td>Non–HDL-C &lt; 156</td>
<td></td>
<td>19.8</td>
<td>15.2</td>
<td>28</td>
</tr>
<tr>
<td>Non–HDL-C ≥ 156</td>
<td></td>
<td>27.2</td>
<td>22.3</td>
<td>25</td>
</tr>
<tr>
<td>TGs &lt; 178</td>
<td></td>
<td>22.8</td>
<td>16.8</td>
<td>30</td>
</tr>
<tr>
<td>TGs ≥ 178</td>
<td></td>
<td>27.6</td>
<td>24.1</td>
<td>17</td>
</tr>
</tbody>
</table>

Abbreviation: RRR, relative risk ratio.

took atorvastatin, whose plaque volume remained stable (mean LDL-C, 79 mg/dL). Although the clinical meaning of these differences are not clear, the fact that more intensive statin therapy modified plaque behavior beyond that achieved by pravastatin, 40 mg per day—an intervention that demonstrated effectiveness in primary and secondary prevention trials—is provocative and raises the possibility that increased LDL-C lowering or maximized statin therapy (or both) may yield greater benefit than submaximal treatment.

PROVE-IT was a much larger clinical outcomes trial that tested the same question. In this study, 4162 subjects (18% had diabetes) who presented with an acute coronary syndrome were randomized to the same two treatments as in REVERSAL for an average period of follow-up of 30 months [41]. Subjects who took atorvastatin achieved a median LDL-C of 65 mg/dL and had a significant ($P < .005$) reduction in deaths and major cardiovascular events after 2 years compared with those who took pravastatin (median LDL-C, 99 mg/dL). This finding supports the concept that in very high-risk subjects, intensive statin therapy was more effective in reducing coronary events. Diabetic subjects who have established CVD reasonably could be included in such a group. Whether the findings from these short-duration trials might reflect so-called “pleiotropic statin effects” in addition to the lowering of LDL-C is conjectural. The results of similar long-term comparative statin trials, using conventional clinical end points, that are conducted in patients who have stable CHD are awaited eagerly.

**Fibrates**

There have been three clinical intervention trials that used fibrate monotherapy and included a subgroup of diabetic individuals. Neither the Helsinki Heart Study, a primary prevention study with gemfibrozil [42], nor the Bezafibrate Infarction Prevention (BIP) trial, a secondary prevention study [43], both with small diabetic subgroups, demonstrated a significant benefit of fibrate treatment in diabetic subjects; bezafibrate did not reduce CVD outcomes overall in the full cohort of the BIP trial. The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention trial (VAHIT), however, found that treatment with gemfibrozil, 1200 mg per day, in 2531 men who had CHD—25% of whom had diabetes, low HDL-C, and a below average mean LDL-C value (LDL-C, 111 mg/dL)—reduced the risk of CHD death, nonfatal myocardial infarction (MI), or confirmed stroke by 24% in the diabetic and nondiabetic subsets [44]. The only lipid measure that predicted the CVD benefit was the increase in HDL-C (+7%) with treatment. Inclusion of previously undiagnosed diabetic subjects in the group that had established diabetes expanded and confirmed these results, and demonstrated a 37% reduction in the incidence of nonfatal MI or fatal CHD in these patients [45]. In addition, an analysis that included diabetic subjects and nondiabetic subjects who had a marker for insulin resistance demonstrated that the beneficial effect of
gemfibrozil was limited to this combined group (about 50% of the total VAHIT population); this suggested that gemfibrozil was particularly effective in insulin-resistant subjects. In support of the VAHIT results were the findings in the Diabetes Atherosclerosis Intervention Study, which demonstrated an improvement in angiographic stenoses in type 2 diabetic subjects who were treated with fenofibrate [46]. These two studies suggest that gemfibrozil, and possibly, fenofibrate, are effective in reducing CHD events and stroke in diabetic (or nondiabetic insulin-resistant) subjects who had average or below average LDL-C levels and established CVD.

**Niacin**

The Coronary Drug Project, published in 1975, was the only study that evaluated the effect of niacin monotherapy on cardiovascular events [47]. In this study, 1119 men who had a history of MI were allocated to treatment with niacin, 1 g to 3 g per day, and 2789 participants received placebo. The mean baseline total cholesterol and triglyceride values were 250 mg/dL and 177 mg/dL, respectively. Despite a lack of benefit on total mortality, the risk of recurrent nonfatal MI was reduced by 27% with niacin. A recent reanalysis of the data showed that the benefit of niacin treatment on recurrent MI was similar at all levels of blood glucose, including patients whose fasting blood glucose was greater than 126 mg/dL [48]. Evidence for a beneficial effect from the addition of niacin therapy to statin treatment was suggested by the HDL Atherosclerosis Treatment Study (HATS) [49]. The effect of combination therapy (simvastatin plus niacin) on angiographic end points was compared with placebo in 160 individuals who had CHD and low HDL-C levels; 16% had diabetes. Simvastatin plus niacin resulted in a significant angiographic benefit with some regression of lesions, an effect that has not been documented clearly with statin therapy alone. Furthermore, despite the small sample size, treatment with niacin plus simvastatin was associated with a significant (60%) reduction in cardiovascular events (CHD death, nonfatal MI, stroke, or revascularization for worsening ischemia), which is a numerically greater effect than was demonstrated in statin monotherapy trials, with the exception of the hypercholesterolemic 4S diabetic subgroup.

**National Cholesterol Education Panel Adult Treatment Panel III Guidelines**

In the original NCEP ATP III guidelines [9], diabetes is considered to be a CHD equivalent. The lipid targets for individuals who have diabetes are the same as for individuals who have established CHD; the primary target is an LDL-C of less than 100 mg/dL [9]. In a recent update [50], ATP III modified the cut point for LDL-C lowering by pharmacotherapy in
high-risk patients from an LDL-C of more than 130 mg/dL to an LDL-C of more than 100 mg/dL, based mainly on the HPS results. In addition, they proposed a new category of very high-risk patients, included among whom are diabetic subjects who have CVD, in which the option of an LDL-C target of 70 mg/dL for statin therapy might be expected to yield additional benefit. They did note that in diabetic subjects who did not have CHD and whose LDL-C was less than 116 mg/dL, the effect of statin treatment in HPS was only marginal (RRR 30%, \( P = .05 \)), and thus, clinical judgement was needed to be exercised at this level. The ATP III panel pointed out that some diabetic subjects may not have a CHD risk equivalent (eg, younger patients and those who do not have other CVD risk factors, in whom an LDL-C > 130 mg/dL might be a more appropriate cut point for pharmacotherapy). They also proposed that a minimal “standard” statin dose be chosen if CVD prevention is to be successful (ie, at least 30%–40% decrease in LDL-C) (Box 1).

For individuals who have triglyceride levels of greater than 200 mg/dL, a secondary lipid target that was proposed originally by the ATP-III panel is the non–HDL-C (total cholesterol minus HDL cholesterol). Non–HDL-C correlates well with apo B and includes all atherogenic lipoproteins that contain apo B 100 (ie, LDL, lipoprotein (a), intermediate-density lipoprotein [IDL], and VLDL). The goal set for non–HDL-C is 30 mg/dL higher than the LDL target (< 130 mg/dL for diabetic subjects), although the update panel did not discuss decreased cut points or targets for non–HDL-C in those groups of subjects for whom new, lower LDL-C treatment cut points and goals are recommended. When triglyceride values are at least 500 mg/dL, the first priority is to lower triglyceride levels because of the risk of pancreatitis. HDL-C is the third lipid target and HDL-C increasing strategies may be considered in “high risk” individuals who have HDL-C levels that are less than 40 mg/dL. In the ATP III guidelines, however, HDL-C target levels were not established because of the lack of definitive information regarding the benefit of increasing HDL-C.

**American Diabetes Association guidelines**

The American Diabetes Association (ADA) categorizes diabetic individuals into low, intermediate, and high CHD risk based on their lipid profiles. The desirable LDL-C, HDL-C, and triglyceride levels are less than 100 mg/dL, more than 40 mg/dL in men/more than 50 mg/dL in women, and less than 150 mg/dL, respectively. The primary treatment strategy, as in NCEP ATP III, is decreasing LDL-C to less than 100 mg/dL (Table 3). The recommended LDL-C level to start pharmacologic therapy is more than 100 mg/dL in individuals who have established CHD and at least 130 mg/dL in those who do not have CHD. The 2004 recommendations also state that “statin therapy to achieve an LDL-C reduction of ~30% regardless of
baseline LDL-C levels may be appropriate” based on the HPS results in diabetic subjects who were older than 40 years of age and who had a total cholesterol of at least 135 mg/dL. The second lipid strategy is increasing HDL-C with a target of more than 40 mg/dL for men and more than 50 mg/dL for women; the third priority is decreasing triglyceride to less than 150 mg/dL. These targets, however, are not based solely on results of clinical trials, but are arbitrary cut points that are used to separate ranges of values that are considered “acceptable” or “at increased risk.” The ADA guidelines also emphasize the importance of glycemic control and lifestyle interventions, such as weight loss, exercise, and smoking cessation in the management of hypertriglyceridemia and low HDL-C levels [51].
American College of Physicians guidelines

The American College of Physicians (ACP) recently published its review and report on the management of LDL-C in type 2 diabetes [52]. Their recommendation was that all subjects who have CHD should be on lipid lowering-therapy, with statins as the primary agent of choice. For individuals who do not have CHD or those who have other CVD risk factors also are recommended for pharmacotherapy, and like ATP III and the ADA, the ACP endorsed the use of at least a moderate dosage of statin.

Table 3
Treatment decisions by low-density lipoprotein cholesterol levels in adults who have diabetes

<table>
<thead>
<tr>
<th>Status</th>
<th>Therapy (mg/dL)</th>
<th>Medical nutrition</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initiative level</td>
<td>LDL-C goal</td>
<td>Initiative level</td>
</tr>
<tr>
<td>With CHD, PVD, or CVD</td>
<td>&gt; 100</td>
<td>≤ 100</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Without CHD, PVD, and CVD</td>
<td>&gt; 100</td>
<td>≤ 100</td>
<td>≥ 130a</td>
</tr>
</tbody>
</table>

Recent findings from the Heart Protection Study [37,38], in people with diabetes over the age of 40 years with a total cholesterol ≥ 135 mg/dL, suggest that statin therapy to achieve an LDL reduction of ~30% regardless of baseline LDL levels may be appropriate.

Abbreviation: PVD, peripheral vascular disease.

a In patients with LDL between 100 mg/dL and 129 mg/dL, a variety of treatment strategies are available, including more aggressive MNT and pharmacologic treatment with a statin.


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Therapeutic interventions

Lifestyle modification

Nutrition therapy is essential in the management of diabetic dyslipidemia. NCEP and ADA guidelines both recommend reducing the intake of saturated fatty acids and transsaturated fatty acids to decrease LDL-C levels [9,50,53]. ATP III recommends limiting the intake of saturated fat to less than 7% of the daily calories and the intake of cholesterol to less than 200 mg/d. This diet, also known as the Step 2 diet, was shown in a meta-analysis to be associated with a 16% reduction in LDL-C [54]. Additional dietary options to decrease LDL-C include increasing the amount of soluble dietary fiber to 10 g/d to 25 g/d, adding 2 g/d of plant stanols/sterols, and including soy protein in the diet. These interventions have been associated with an additional 5% to 15% reduction in LDL-C values [55–57].

The distribution of macronutrients in the diet is a matter of debate, particularly in individuals who have diabetic dyslipidemia. Low-fat, high-carbohydrate (> 60% of total caloric intake) diets have been associated with an increase in triglyceride and a decrease in HDL-C levels [58]. When monounsaturated fat is substituted for saturated fat in the diet, the LDL-C
lowering effect is similar to that obtained with a low-fat, high carbohydrate diet without the increase in triglyceride and the decrease in HDL-C levels [59,60]. Therefore, ATP III recommends limiting the intake of carbohydrates to less than 60% in individuals who have the metabolic syndrome, which is present in more than 80% of people who have type 2 diabetes. Furthermore, for individuals who have elevated triglyceride and low HDL-C levels, even lower carbohydrate intake (ie, < 50% of calories) could be considered. The ADA also recommends replacing saturated fat with carbohydrates or monounsaturated fat [53]. Low carbohydrate diets have been used for many years and recently have become even more popular. Although these diets may have short-term beneficial effects on serum lipids, fasting glucose, and weight reduction, these benefits have not been shown to persist over a more lengthy period [61]. Furthermore, low carbohydrate diets have not been evaluated adequately in individuals who have diabetes and hyperlipidemia; their long-term safety and efficacy remain unknown.

Exercise and pharmacologic approaches to weight loss in overweight individuals who have diabetes also are important strategies in the management of atherogenic dyslipidemia. The predominant effect of exercise is on maintaining or achieving weight reduction targets and its most consistent effect on lipids is to increase HDL-C. Lastly, supplementing the diet with omega-3 fatty acids (3–8 g/d) is another intervention that decreased triglyceride levels by 15% to 30% in diabetic subjects in short-term studies without significant adverse effects on hemoglobin A1c (HbA1c) or HDL-C, and only a slight increase in LDL-C values [62,63].

**Pharmacologic treatment**

**Oral antihyperglycemic agents**

Improved glycemic control, regardless of type of treatment, is associated with improved lipid values in individuals who have moderate to severe hyperglycemia. In the Veterans Affairs Cooperative Study in Type II Diabetes, intensive glycemic control with insulin therapy that resulted in a reduction of HbA1c from 9.3% to 7.2% was associated with a 31% decrease in triglyceride levels after 1 year, and a 23% reduction at 2 years without a significant change in LDL-C or HDL-C [64]. Beyond its effects on glycemic control, metformin was associated with a modest reduction in triglyceride levels in hyperlipidemic and hypertensive patients who did not have diabetes, as well as in some, but not all, studies of diabetic subjects who received monotherapy or in combination with sulfonylureas [65]. Changes of lesser magnitude in LDL-C and HDL-C also were reported with metformin treatment in some of these studies. Rosiglitazone and pioglitazone increased HDL-C and reduced the density of LDL particles [66–69]. Pioglitazone seemed to have a neutral effect on LDL-C concentration and a moderate reduction in triglyceride levels, whereas rosiglitazone elevated LDL-C modestly [67]. In general, pioglitazone seems to be associated with
more beneficial lipid effects than rosiglitazone in published small studies. This was confirmed by a recently reported double-blind, randomized, head-to-head 24-week treatment comparison study of pioglitazone versus rosiglitazone in moderately hypertriglyceridemic type 2 diabetic subjects not receiving other antihyperglycemic or lipid-modifying agents. Pioglitazone was associated with significant triglyceride reduction whereas there was no net triglyceride change with rosiglitazone treatment. In addition, pioglitazone was associated with greater increases in HDL-C and LDL particle size, and less LDL-C increase than with rosiglitazone. Furthermore, apo C-III and LDL particle number increased with rosiglitazone therapy, but decreased with pioglitazone. These results suggest a beneficial antidyldlpidemic effect of pioglitazone [70].

Pharmacologic lipid-modifying strategies

The NCEP and the ADA have given first priority to the achievement of LDL-C targets that recommend that many, if not most, subjects be treated with LDL-C-lowering medication if their LDL-C levels are more than 100 mg/dL and advise statin therapy for all diabetic subjects whose LDL-C levels are more than 130 mg/dL. At levels between 100 mg/dL and 129 mg/dL—where both sets of guidelines previously had deferred from making firm pharmacotherapeutic recommendations (except for the ADA in subjects who had CVD)—now both guidelines generally are supportive of statin therapy at a level that is likely to achieve at least a 30% to 40% decrease in LDL-C. Furthermore, both guidelines open the way to initiating pharmacotherapy with statins, essentially independent of the LDL-C, in subjects who are deemed to be at high or very high risk; the NCEP report set an optional goal of 70 mg/dL in the latter group of individuals. Because almost 80% of subjects who have diabetes have LDL-C levels that are more than 100 mg/dL [13], these proposals and the robustness of the clinical trial data that underpin them support the initiation of lipid-lowering pharmacotherapy with at least a moderate dosage of statin (rosuvastatin 5–10 mg/d; atorvastatin 10–20 mg/d; simvastatin 20–40 mg/d; and pravastatin, lovastatin, and fluvastatin 40–80 mg/d) in most diabetic subjects; subjects who have CVD should be considered for maximal intensity statin and or combination therapy. Although diabetic subjects who did not have CVD and whose LDL-C levels were less than 116 mg/dL obtained only borderline benefit from simvastatin in HPS, a similar group that received atorvastatin in the CARDS trial achieved a significant 27% reduction in major events (P = .025). This strengthens the case for initiating statin therapy, even in subjects (> 40 years of age) who have a low LDL-C and who do not have heart disease, as long as they have at least one major risk factor.

What are the exceptions to these recommendations? One of these is the individual who has severe hypertriglyceridemia (> 400–500 mg/dL), in whom fibrates are more effective in reducing markedly elevated triglyceride values. Another exception might be in diabetic subjects whose cardiovascular risk is
deemed not to be high within the forthcoming decade (eg, type 1 diabetes and recent-onset type 2 diabetes in persons who are younger than 30 years of age), especially if there are no risk factors or presence of the metabolic syndrome. Although this age-based cut point seems reasonable for type 1 diabetic subjects, based on studies of CVD incidence as a function of age [61,62], there is little information on the risks of cardiovascular disease in the increasingly important type 2 diabetic subgroup in this age category. In a recent comparison of macrovascular event rates in subjects who had newly-diagnosed type 2 diabetes who were less than 45 years of age (mean age, 38 years) and older than 45 years of age (mean age, 60 years), event rates were five-fold greater in the older age group over a 4-year period of follow-up [71]; this attests to the powerful effect of age on CVD incidence in diabetic subjects.

Near-routine prescription of a statin for diabetic patients creates a significant dilemma in regard to the place of fibrates and of niacin, both of which demonstrated CVD benefit in monotherapy trials in subjects who had established CHD. One option is to use these agents in combination with statins; it is clear that statin-treated patients continue to have CVD events, albeit at a lower rate than untreated individuals. Conversely, these drugs may interact with statins and occasionally cause serious complications. There is no evidence that combination therapy provides further benefit over effective monotherapy with statins; it is difficult to justify using these combinations routinely. Viewed in these terms, pharmacotherapeutic decision-making for diabetic dyslipidemia essentially boils down to the following questions: Which agent should be used to initiate therapy and what should be the goal be? When should statin/fibrate, statin/niacin, or other drug combinations be used? There are little to no clinical trial data to help with the answers to these questions; a pragmatic approach based on available evidence and clinical judgment is proposed.

**Initiating therapy in subjects whose low-density lipoprotein cholesterol is at least 130 mg/dL**

Clinical trial studies demonstrate a clear benefit of statin treatment at LDL-C levels of at least 130 mg/dL; there is little controversy about initiating statin therapy in this situation. Moreover, the VAHIT study did not test the effect of fibrates in subjects whose LDL-C values were at least 130 mg/dL. In the BIP study, bezafibrate did not show any benefit in subjects whose mean LDL-C was approximately 149 mg/dL, so there is less support for initiating therapy with fibrates in dyslipidemic subjects whose LDL-C is more than 130 mg/dL. Finally, niacin therapy alone, which reduces LDL-C by 10% to 20%, would be inadequate for reaching LDL-C targets in many of these individuals. Statins reduce LDL-C by 20% to 55% and have a good safety and tolerability profile; effects on muscle and on liver enzyme levels are the most important safety concerns. Elevation of liver enzymes to more than three times the upper limit of normal (ULN) was
reported in less than 1.5% of participants, and clinical significant myopathy (creatine kinase ≥ 10 × ULN) was reported in less than 0.3% of participants in large clinical trials (both nonsignificantly different from placebo) [38,72]. The risk of myopathy increases with the concomitant use of medications that inhibit the metabolism of statins. Therefore, potent inhibitors of the cytochrome CPY3A4 system (eg, cyclosporine, gemfibrozil, ketoconazole, itraconazole, erythromycin, clarithromycin, indinavir, nelfinavir, nefazodone) should be avoided, particularly with simvastatin, atorvastatin and lovastatin. Pravastatin, fluvastatin, and rosuvastatin are not metabolized significantly by the cytochrome CPY3A4 enzymes and are not known to interact with the above medications. The combination of a statin with ezetemibe is likely to be effective in achieving LDL-C goals of approximately 70 mg/dL; the availability of single-tablet fixed combinations of simvastatin plus ezetemibe (Vytorin) should be helpful in this regard. A more potent statin also is more likely to achieve optimal lowering of LDL-C and non–HDL-C. When the NCEP LDL-C target is not achieved with a statin alone, or in cases in which statins are not tolerable, combination therapy with ezetimibe, bile acid sequestrants, or niacin may be effective; each agent reduces LDL-C by 10% to 20%.

Initiating therapy in subjects whose low-density lipoprotein cholesterol is less than 130 mg/dL

Although for some time the ADA has recommended starting a statin when LDL-C is more than 100 mg/dL in diabetic patients who have established CHD, there have been no other firm recommendations in favor of pharmacotherapy for subjects whose LDL-C is less than 130 mg/dL until recently, although ATP III did suggest statin or fibrate therapy as options in this LDL-C range. The recent ATP III update supports statin therapy in this LDL-C range in high-risk subjects, based on the more recent statin trials, and does not specifically mention fibrates in this connection as an alternate first option (unless there is significant hypertriglyceridemia). The ADA guidelines state that statin treatment now may be considered, irrespective of the LDL-C value, in view of the positive HPS results in this group of patients. Clinical data from VAHIT, however, support the use of gemfibrozil in diabetic patients who have coronary artery disease and dyslipidemia and less than average LDL-C and minimally elevated triglyceride levels. On this basis, NCEP ATP III included statin and fibrate therapy as options for these individuals when the LDL-C is 100 mg/dL to 129 mg/dL. Thus, in this group of subjects, the clinician is faced with the dilemma of choosing between a fibrate or a statin, or for that matter, between a statin and niacin as first-line therapy. Several points need to be made in this regard.

It has been argued that gemfibrozil was more effective in reducing “hard” CHD events and strokes in dyslipidemic subjects who had below average
LDL-C values and diabetes or features of the metabolic syndrome in the VAHIT, than statins were in the CARE, LIPID, and Anglo-Scandinavian Cardiac Outcomes Trials [73]. In addition, because statin therapy does not seem to especially benefit insulin-resistant subjects, whereas gemfibrozil seemed to, it was proposed that gemfibrozil treatment should be favored over statins in dyslipidemic diabetic subjects whose LDL-C values were less than 130 mg/dL [73]. In the larger statin studies, such as HPS and now in CARDS, however, statin treatment was about as or more efficacious than gemfibrozil in VAHIT, not only in those who had CVD, but also in subjects who did not have established CVD. Only a single, positive, event-based fibrate study has been conducted in diabetic subjects; all had established CVD, which limits the evidence base in support of fibrate therapy.

It also can be argued that fibrates modify the dyslipidemia that is typical of diabetes more effectively than statins. Fibrates decrease triglyceride (25%–50%) and increase HDL-C (7%–15%) levels better than do statins, although the way in which they do this differs. Statins act principally by up-regulating the LDL receptor and enhancing clearance of apo B 100–containing lipoproteins, whereas fibrates exert their action by activating peroxisome proliferator-activated receptor–α (PPARα), which has multiple effects on triglyceride-rich lipoprotein metabolism, especially their clearance. Fibrates increase LDL particle size distribution better than statins. This may be, in part, because they reduce triglyceride levels more than statins do; however, the relationship of these changes to their CVD benefit is not known. It seems that at least within a large population of diabetic subjects, the LDL-C level is the most powerful predictor of CVD; fibrates do not decrease LDL-C significantly in dyslipidemic subjects. The tendency to recommend statin therapy for reduction of elevated LDL-C levels, and fibrate therapy for hypertriglyceridemia, is no longer tenable following the recognition that LDL-C levels below average may continue to exert atherogenic effects, and that intensive statin therapy decreased triglyceride, VLDL levels, and remnant lipoproteins significantly. Conversely, the benefit that was attributed to gemfibrozil in VAHIT was demonstrated in subjects who did not have definitive hypertriglyceridemia and was not related to decreases in triglyceride. It also was pointed out that although most of the CVD benefit in statin trials can be related to their major effect on lipids (ie, decreasing of LDL-C), the effect of gemfibrozil on the lipid profile cannot explain much more than 25% of the CVD benefit [73]. Presumably, the bulk of the benefit would be explained by other cardioprotective PPARα effects of gemfibrozil, related to its actions on inflammatory processes and the vascular wall; not understanding the mechanisms that are involved adds to the difficulty in resolving this issue. Fibrates and statins rarely are reported to cause rhabdomyolysis.

The case for niacin is weaker, by virtue of the fact that a significant number of individuals are not able to tolerate an effective dosage, notwithstanding the
recent data that demonstrated the usefulness of niacin preparations in the treatment of dyslipidemia in diabetic subjects. Furthermore, the evidence base for CVD benefit in diabetic subjects is limited. Until a direct comparative intervention trial is completed (not until 2009), the question as to whether combination therapy has significant clinical benefits over monotherapy will remain unresolved. On balance, the robustness of the clinical trial data, the extensive clinical experience with statins, and the wealth of data that support their antiatherogenic activity tends to support initiation of therapy with statin drugs, rather than fibrates or niacin, in subjects whose LDL-C is less than 130 mg/dL, except in those who have severe hypertriglyceridemia. One of the more potent statins is preferred to make it more likely that effective decreases in LDL-C and non–HDL-C triglyceride is achieved.

**Secondary targets: beyond decreasing low-density lipoprotein cholesterol**

Non–HDL-C is the focus of the secondary therapeutic strategy that was proposed by ATP III in the management of dyslipidemia, after the LDL-C goal is achieved and when triglyceride levels are at least 200 mg/dL. There is now evidence in diabetic subjects that non–HDL-C values are more predictive of CHD rates than are LDL-C levels[74]. The ADA guidelines recommend decreasing triglyceride levels to low-risk targets (ie, < 150 mg/dL), although it is not known whether decreasing non–HDL-C or triglyceride levels are correlated independently with CVD benefit. Although gemfibrozil decreased triglyceride levels significantly in the VAHIT study in the absence of a change in LDL-C and in which the baseline triglyceride was less than 200 mg/dL, this did not correlate with the CVD benefit. Fibrates do not change non–HDL-C significantly unless the triglyceride level exceeds 250 mg/dL to 300 mg/dL; therefore, this ATP III measure has little practical value as a cut point or target for fibrate therapy in the average patient who has diabetes. Statins are the most effective agents for decreasing levels of non–HDL-C. In addition to statins’ LDL lowering effects, they also reduce VLDL cholesterol and IDL cholesterol, probably by enhancing their removal rates by way of the LDL-receptor, although it was suggested that at high dosages, statins may reduce VLDL secretion as well[75]. Therefore, even if LDL-C levels are decreased to target levels on statin therapy, increasing the dosage of statin, switching to a more potent statin, or adding ezetemibe would achieve greater non–HDL-C and triglyceride lowering and help to achieve secondary lipid lowering goals. Furthermore, if significant triglyceride lowering is achieved with high-dose statins, an increase in LDL particle size may be achieved[76]. In addition, treatment with statins also results in a greater reduction of the total number of LDL particles and apo B concentration than other agents. It has been argued that apo B may be a better marker of dyslipidemia than non–HDL-C[77–79]; in either case, statin therapy seems to be a first choice in pharmacotherapy. These considerations tend to marginalize fibrates for the most part to combination
therapy. Finally, on the issue of increasing HDL, ATP III indicates that in high-risk subjects whose HDL-C levels that are less than 40 mg/dL, as a third priority, consideration should be given to the use of niacin and fibrates, although no goal for HDL-C is defined. Similarly, the ADA indicates that increasing HDL-C may be considered in subjects who have high-risk levels of HDL-C (ie, HDL-C values of < 40 mg/dL in men and < 50 mg/dL in women), without defining targets. Although there is widespread interest in increasing HDL-C, the current limitations in being able to increase HDL-C significantly, as well as the gaps in the understanding of the consequences of HDL-increasing interventions on atherogenesis, make it premature to construct formal recommendations. This does not imply that fibrates and niacin, the two agents that are recommended most commonly for increasing HDL, do not have value in the treatment of dyslipidemia.

Combination therapy

The concept that underlies the addition of a second or third agent is to optimize improvements in the lipid profile that is achieved by initial statin therapy. That further CVD prevention methods are needed is without doubt, in view of evidence such as that in the HPS, which noted an almost 20% 10-year event rate in the simvastatin-treated cohort that had diabetes and no baseline evidence of CVD [37]. In terms of the NCEP and ADA guidelines, this means decreasing LDL-C at least to less than 100 mg/dL, reducing non–HDL-C values to less than 130 mg/dL and triglyceride values to less than 150 mg/dL, and increasing HDL-C levels to more than 40 mg/dL (or > 50 mg/dL in women, according to ADA). This strategy is based on the empiric assumption that further improvement in the lipid profile, beyond that which was achieved initially with monotherapy, will yield additional CVD benefit. There are no data from a controlled clinical trial that compared monotherapy with combination treatment. It was shown clearly that the addition of ezetimibe to a statin will decrease LDL-C and non–HDL-C to NCEP goals in more individuals than a statin alone will do [80]. Ezetimibe, an intestinal inhibitor of cholesterol absorption, was associated with an additional 15% to 20% reduction in LDL-C levels among individuals who had hypercholesterolemia, had modest beneficial effects on triglycerides and HDL-C, and was well-tolerated [80]. Bile acid sequestrants also may help to decrease LDL-C but should be used with caution because they increase triglyceride levels in hypertriglyceridemic subjects [81].

It also is clear that achievement of all three lipid goals is more likely with statin plus fibrate or statin plus niacin combinations [82–84]. The added complexity and risks of combination therapy, in the absence of persuasive clinical trial evidence for additional CVD benefit, however, must place some limitations on the use of these combinations. The presence of CVD or severe metabolic syndrome seems to be a strong indication for combined therapy in patients who have diabetes, as perhaps should be the presence of hypertension, albuminuria, smoking, and a increased serum creatinine.
Statin-niacin combination therapy

The addition of niacin to statin therapy has a significant lipid-modifying benefit because niacin decreases triglycerides by 20% to 50% (upper limit requires high dosages of niacin), reduces LDL-C by 5% to 25%, increases HDL-C by 15% to 35%, and decreases non–HDL-C moderately. Thus, addition of niacin to a statin may be helpful in achieving LDL-C and non–HDL-C goals. Niacin increases HDL-C to a greater extent than any other agent. Although the benefits of increasing HDL-C levels are not well-understood and pharmacologic agents that affect HDL-C values also have effects on other lipoproteins, the VAHIT and HATS studies are supportive of this strategy. At high dosages, niacin decreases lipoprotein (a) values up to 30% [85]. Triglyceride decreases result in a shift in LDL and HDL particle density from small dense to larger, more buoyant particles [86]. Moreover, the HATS trial demonstrated that the combination of simvastatin and niacin was effective in reducing CVD events [49]. Niacin has significant adverse effects, however. The most common is an unpleasant flushing or tingling, particularly at higher dosages, and stepped titration of the dose is required, thus increasing the time and effort that is required from the medical team. Hepatotoxicity is the most important of the side effects, particularly with “long-acting” or “sustained release” niacin preparations that use dosages of more than 2000 mg daily [87]. The extended release once-a-day preparation of niacin (Niaspan) has been found to be effective and safe with a low incidence of hepatotoxicity [88]. Rare cases of myopathy were reported with the combined use of niacin and lovastatin [89], but have not been described in studies of Niaspan and lovastatin in a single tablet formulation [84]. The incidence of myopathy that is associated with the combination of niacin and statins seems to be significantly less than with statins and gemfibrozil [92]; this supports the case for greater safety with the former combination. Past use of niacin in diabetic patients has been limited because of concerns that this agent may lead to deterioration in glucose control. Recent studies showed only modest increases in HbA1c values in patients whose diabetes was well-controlled and who received up to 3000 mg of immediate-release niacin [91] and up to 1500 mg of Niaspan [88]. Dosages as small as 1000 mg per day may increase HDL-C moderately. Nevertheless care should be exercised when using this agent in diabetic subjects; it probably is wise to delay niacin therapy until glycemic control is improved if the HbA1c level is more than 8.0%.

Statin-fibrate combination therapy

The addition of a fibrate to statin treatment achieved ADA goals in most diabetic subjects who received it [82,83]. Combination treatment with a statin and a fibrate should be used with caution because the risk of myopathy is increased, particularly in individuals who have predisposing conditions like renal failure [90]. Myopathy and rhabdomyolysis were reported in the published literature with simvastatin, cerivastatin, lovastatin,
atorvastatin plus gemfibrozil, and pravastatin plus fenofibrate [93–97]. Several short-to-medium term studies (N = 81–420) that evaluated the efficacy and safety of different statin-fibrate combinations in patients who had combined hyperlipidemia showed additive effects on lipids and lipoproteins, a low incidence of clinically significant myopathy, and no case of rhabdomyolysis [98–102]. The absence of severe myositis in these studies is not surprising in view of its selective and low incidence, even in combination therapy. Recently, it was demonstrated that gemfibrozil and fenofibrate differ in their effects on statin pharmacokinetics. Gemfibrozil significantly inhibited the glucuronidation of statins—an important but previously unrecognized metabolic pathway of statin catabolism—whereas fenofibrate had little effect [103,104]. This probably explains why plasma statin levels are increased significantly with gemfibrozil treatment and not with fenofibrate. Thus, fenofibrate is preferred to gemfibrozil for use in combination therapy with statins, despite the fact that clinical trial data that support its use are less robust. It also should be pointed out that several cases of fenofibrate monotherapy–associated rhabdomyolysis have been reported in the literature [105]. Thus, a risk of rhabdomyolysis is associated with fenofibrate therapy. A recently reported national survey of the prevalence of rhabdomyolysis associated with statin-fibrate combination therapy estimated that the prevalence of rhabdomyolysis was approximately 10 times more frequent with statin plus fenofibrate treatment than statin monotherapy and about a 100 times more likely with statin plus gemfibrozil treatment compared with statin monotherapy [106]. Whether combination with statin drugs increases this risk, as apparently is true for gemfibrozil, is unknown. In the ATP III update, wider use of the statin-fenofibrate combination is mentioned based on the supposition that fenofibrate will be less likely to cause rhabdomyolysis, in combination with statin treatment, than gemfibrozil. Finally, fenofibrate is more likely to increase serum creatinine levels than is gemfibrozil and should be avoided in patients who have renal disease; in these patients, the combination of statin and niacin probably is safer than a statin-fibrate regimen.

References


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