

# Treating Diabetic Dyslipidemia: A Review of Practical Recommendations Based on Clinical Trials

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**H**ear disease mortality in the United States has fallen substantially in the last several decades, primarily due to reductions in cardiovascular risk factors and improvements in heart disease treatments.<sup>1</sup> Whether patients with diabetes mellitus (DM) have experienced a decline in heart disease mortality similar to that in the general US population has been a subject of debate. In relative terms, DM confers a twofold greater risk of cardiovascular disease (CVD)<sup>2</sup> and mortality in the year following a myocardial infarction (MI), and in patients who survive to day 28 post-MI, the risk is approximately 2 times higher in men and 4 times higher in women with DM compared with their nondiabetic counterparts.<sup>3</sup> The fact that the rates of type 2 DM, metabolic syndrome, and obesity continue to rise<sup>4,5</sup> provides an additional impetus for more targeted and aggressive management of cardiovascular risk factors in patients with DM.

In the majority of patients, the characteristic cardiovascular risk factors in type 2 DM include hyperglycemia, hypertension, modestly increased levels of low-density lipoprotein cholesterol (LDL-C), and decreased levels of high-density lipoprotein cholesterol (HDL-C).<sup>6</sup> Decreased HDL-C along with elevated triglycerides and small, dense LDL-C particles are the characteristic features of diabetic dyslipidemia, which substantially increases the risk of CVD in patients with DM.<sup>7</sup> Thus, intensive glycemic control alone is not likely to eliminate the excess risk of CVD in these patients.<sup>8</sup> A multifactorial approach is warranted, as supported by results of the Steno-2 study.<sup>9</sup> The high cardiovascular risk associated with DM warrants more aggressive lipid-lowering therapy, including reduction of LDL-C, in all patients with DM.

Interestingly, LDL-C levels in patients with DM are typically not higher than LDL-C levels in matched controls and are often in the range that has been described as "borderline high" (ie, 130–159 mg/dL).<sup>7</sup> However, other metabolic abnormalities also contribute to the increased CVD risk that accompanies DM. For example, aside from the absolute LDL-C level, the number of low-density lipoprotein particles is typically greater than sug-

## TAKE HOME POINTS

- Diabetes mellitus (DM) is now recognized as a risk equivalent for coronary heart disease.
- The lipid profile in patients with type 2 DM is characterized by elevated triglycerides, low levels of high-density lipoprotein cholesterol, and small, dense low-density lipoprotein cholesterol (LDL-C) particles and is believed to be a key factor promoting atherosclerosis in these patients.
- Both secondary and primary prevention studies have provided evidence that aggressive statin therapy reduces cardiovascular end points in patients with DM.
- In all persons with DM, current treatment guidelines recommend reduction of LDL-C to less than 100 mg/dL, regardless of baseline lipid levels.
- Lowering LDL-C to less than 70 mg/dL may provide even greater benefits, particularly in very high-risk patients (eg, patients with DM and existing cardiovascular disease or those who smoke).

gested by the LDL-C level alone, as particles are smaller and denser in patients with DM than in the general population.<sup>7</sup> It is also likely that synergistic interactions between modest elevations in LDL-C and other risk factors associated with the metabolic syndrome, which is common in persons with type 2 DM, enhance the pathophysiologic importance of LDL-C in this disease.<sup>7</sup> Together these findings support LDL-C as a primary target of cardiovascular risk management in patients with DM. This article reviews practical recommendations for managing dyslipidemia in patients with DM based on results of many large epidemiologic and clinical trials.

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**Table 1.** Epidemiologic Studies Supporting Diabetes as a Coronary Heart Disease Risk Equivalent

Study	Objective	N/Patients with DM (or IFG)	Duration of Study	Results
East-West Study <sup>10</sup>	To determine whether patients with DM and no MI should be treated as aggressively as patients without DM with MI	2432/1059	7 yr	Diabetic patients without previous MI have as high a risk for MI (20%) as nondiabetic patients with previous MI (19%)
OASIS Registry <sup>11</sup>	Prognosis of patients with and without DM with unstable angina or non-Q-wave MI	8013/1718	2 yr	After hospitalization for unstable CAD, patients with DM and no history of CVD have the same long-term morbidity and mortality as nondiabetic patients with established CVD
FINMONICA <sup>3</sup>	Overall 28-day and 1-yr mortality following first MI in patients with and without DM	4065/620	5-yr enrollment, 1-yr follow-up	Patients with DM have a higher mortality rate after first MI and a large proportion of out-of-hospital deaths

CAD = coronary artery disease; CVD = cardiovascular disease; DM = diabetes mellitus; FINMONICA = Finnish Multinational MONItoring of Trends and Determinants in Cardiovascular Disease; IFG = impaired fasting glucose; MI = myocardial infarction; OASIS = Organization to Assess Strategies for Ischemic Syndromes.

## TREATMENT RECOMMENDATIONS

### Treat Patients with DM as if They Have Established Coronary Heart Disease

Two studies reported in 1998, the East-West Study<sup>10</sup> and the Finnish Multinational MONItoring of Trends and Determinants in Cardiovascular Disease (FINMONICA) study,<sup>3</sup> provided evidence for guidelines designating DM as a coronary heart disease (CHD) risk equivalent and for promoting early and aggressive lipid therapy in diabetic patients (Table 1). The East-West Study found that the risk of having a fatal or nonfatal MI over 7 years of follow-up was as high in diabetic patients without a history of MI (20%) as in nondiabetic patients with a history of MI (19%); it also found that diabetic patients with a history of MI are more than twice as likely to die from CHD than nondiabetic patients with a history of MI.<sup>10</sup> These findings were extended to diabetic patients with unstable coronary artery disease in the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry.<sup>11</sup> OASIS showed that among diabetic and nondiabetic patients hospitalized for unstable angina or non-Q-wave MI, persons with DM with no history of CVD had event rates equivalent to persons without DM but with established CVD.

These epidemiologic studies provided evidence that patients with DM and established CVD have a greater risk of dying than their nondiabetic counterparts. Thus, it would seem logical to treat these patients more aggressively in order to lower this excess risk. In addition, because the excess risk occurs early after an MI in those with and without DM, lipid treatment should be initiated early for secondary prevention to provide optimal benefit.

### Aggressively Reduce LDL-C Levels in Patients with DM

Randomized clinical trials of statins provide the best evidence to support aggressive lipid-altering therapy in patients with DM. Major trials of statin therapy that contributed to treatment guidelines for dyslipidemia in diabetic patients are summarized in Table 2 and briefly discussed below.

A post hoc analysis of the Scandinavian Simvastatin Survival Study (4S) provided the first evidence that reducing cholesterol lowers risk in diabetic patients with CHD. There was a large reduction in the primary end point of all-cause mortality in the simvastatin-treated diabetic subgroup (43%) compared with the simvastatin-treated nondiabetic subgroup (29%).<sup>12</sup> Because the absolute risk of CHD was higher in the diabetic subgroup, the absolute benefit of treatment was also greater, a result that was confirmed in the diabetic subgroup of the Cholesterol and Recurrent Events (CARE) study<sup>13</sup> and extended to persons with impaired fasting glucose in another post hoc analysis of 4S.<sup>14</sup>

The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study included substantially more diabetic patients (n = 1077) than either 4S or CARE and also included a large subgroup with impaired fasting glucose (n = 940).<sup>15</sup> Consistent across all end points, risk reductions were greater in patients with impaired glucose than in those with normal fasting glucose.

The Heart Protection Study (HPS) was specifically designed to enroll a large group of diabetic patients (n = 5963), the majority of whom had type 2 DM.<sup>16</sup> Similar to other high-risk subgroups, patients with DM treated with simvastatin had a significant reduction in first

**Table 2.** Trials of Statin Therapy—Prospective and Post Hoc Analyses of Diabetic Subgroups

Study	Agent(s)	Objective	N/Patients with DM (or IFG)	Duration of Study	Results
<b>Placebo-controlled</b>					
4S <sup>12</sup>	Simvastatin 20–40 mg/day versus placebo	Effect of treatment on mortality and CHD risk in patients with previous MI or angina and elevated TC	4444/202	5.4 yr (median)	Statin-treated patients with DM had reductions in all-cause mortality (43%), major CHD events (55%), and any atherosclerotic event (37%) Event reductions were greater in diabetic than in nondiabetic patients
4S <sup>14</sup>	Simvastatin 20–40 mg/day versus placebo	Effect of treatment on mortality and CHD risk in patients with previous MI or angina and elevated TC	4398/ 483 with DM (678 with IFG)	5.4 yr (median)	Simvastatin-treated patients with IFG and CHD had significant reductions in total mortality (43%; $P = 0.02$ ), coronary mortality (55%; $P = 0.007$ ), major CHD events (38%; $P = 0.003$ ), and revascularizations (43%; $P = 0.009$ )
CARE <sup>13</sup>	Pravastatin 40 mg/day versus placebo	Effect of treatment on risk of coronary events in patients with CHD and average cholesterol levels	4139/586	5 yr	Pravastatin treatment in patients with DM reduced the relative risk of CHD events by 25% ( $P = 0.05$ ) and revascularization by 32% ( $P = 0.04$ ) The DM subgroup had a greater absolute reduction in risk of coronary events than the nondiabetic group (8.1% versus 5.2%)
LIPID <sup>15</sup>	Pravastatin 40 mg/day versus placebo	Effect of treatment on risk of CHD death or nonfatal MI and other CV outcomes in patients with CHD and modestly elevated cholesterol	9014/1077 with DM (940 with IFG)	6 yr	Pravastatin reduced major CHD events in subgroups with DM and IFG by 19% ( $P = 0.11$ ) and 36% ( $P < 0.01$ ), respectively, versus a 24% reduction ( $P < 0.008$ ) in the overall study population DM patients had a 21% reduction in risk of any CV event ( $P < 0.008$ ) and a 39% reduction in risk of stroke ( $P = 0.02$ ) Across all end points, risk reductions were greater in those with IFG than in those with normal FG
HPS <sup>16</sup>	Simvastatin 40 mg/day versus placebo	Effect of treatment on first major coronary events and first vascular events in patients with low LDL-C ( $< 135$ mg/dL)	20,536/5963	5 yr	Simvastatin-treated patients with DM had a 22% reduction in first occurrence of major vascular events ( $P < 0.0001$ )
ASCOT—LLA <sup>17,18</sup>	Atorvastatin 10 mg/day versus placebo	Effect of treatment on nonfatal MI and fatal CHD in patients with well controlled hypertension and low TC ( $< 250$ mg/dL)	10,305/2532	3.3 yr (stopped early)	Relative reduction in primary end point was less for diabetics than nondiabetics, but atorvastatin-treated patients with DM had 23% fewer total CV events and procedures than placebo-treated patients (116 versus 151; $P = 0.036$ )
CARDS <sup>19</sup>	Atorvastatin 10 mg/day versus placebo	Effect of treatment in patients with type 2 DM, no CVD, and normal LDL-C	2838 (all with DM)	4 yr median (stopped early)	Atorvastatin-treated patients had a 37% reduction in major CV events versus placebo ( $P = 0.001$ ) and reductions in acute CHD events (36%), revascularizations (31%), stroke (48%), and all-cause mortality (27%; $P = 0.059$ )
<b>Active comparator</b>					
PROVE IT—TIMI 22 <sup>20</sup>	Pravastatin 40 mg/day versus atorvastatin 80 mg/day	Effect of treatment on composite of death, MI, UA requiring rehospitalization, revascularization, and stroke in patients with ACS	4162/734	18–36 mo	Event rates were 26% and 22%, respectively, for the less and more intensive regimens, respectively, reflecting a 16% reduction in the hazard ratio favoring the more intensive regimen; benefit was consistent across groups, including DM patients
TNT <sup>21,22</sup>	Atorvastatin 80 mg versus 10 mg	Efficacy and safety of lowering LDL-C $< 100$ mg/dL in patients with stable CHD	10,001/1501	4.9 yr (median)	Primary event occurred in 8.7% of patients receiving 80 mg versus 10.9% of patients receiving 10 mg (22% reduction in relative risk; $P < 0.001$ ) Patients with DM on more intensive therapy had 25% fewer events than those on less intensive therapy

4S = Scandinavian Simvastatin Survival Study; ACS = acute coronary syndrome; ASCOT—LLA = Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; CARE = Cholesterol and Recurrent Events; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; FG = fasting glucose; HPS = Heart Protection Study; IFG = impaired fasting glucose; LDL-C = low-density lipoprotein cholesterol; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease; MI = myocardial infarction; PROVE IT—TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22; TC = total cholesterol; TNT = Treating to New Targets; UA = unstable angina.

occurrence of major vascular events, including major coronary events, strokes, and revascularizations. Although HPS was mostly a secondary prevention trial, the study enrolled 2912 patients with diabetes but without CVD at baseline.<sup>16</sup> Among these patients, simvastatin therapy reduced the primary end point of first major coronary event by 33% versus placebo. Treatment effect in all diabetic patients was evident regardless of duration, type, or control of DM, age, hypertensive status, or baseline levels of total cholesterol.

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT—LLA)<sup>17</sup> in patients with hypertension and multiple cardiovascular risk factors was stopped after a median follow-up of 3.3 years due to a significant 36% reduction in the primary end point of nonfatal MI and fatal CHD with statin treatment. Among patients with DM, there was a smaller (16%) nonsignificant reduction in the primary end point. Because of the relatively low number of events (84) in patients with DM, the study was thought to be inadequately powered to detect a difference in event rates between diabetics and nondiabetics.<sup>17</sup> However, a subsequent subgroup analysis with a broader cardiovascular end point showed that diabetic patients treated with atorvastatin had significantly fewer cardiovascular events and procedures compared with placebo.<sup>18</sup>

The Collaborative Atorvastatin Diabetes Study (CARDS)<sup>19</sup> was the first study to assess directly the benefits of cholesterol reduction in a cohort entirely comprising patients with type 2 DM ( $n = 2838$ ) without documented CVD and with relatively normal LDL-C levels at baseline. Treatment with atorvastatin 10 mg/day over roughly 4 years reduced the primary end point of major cardiovascular events by 37% versus placebo. Acute CHD events were also decreased (36%), as were coronary revascularizations (31%), stroke (48%), and all-cause mortality (27%).<sup>19</sup>

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT—TIMI 22) study,<sup>20</sup> intensive lipid-lowering therapy was statistically more effective than standard lipid-lowering therapy at reducing the primary end point in diabetic patients hospitalized for acute coronary syndromes. Prespecified subgroup analyses showed that the benefits of intensive statin therapy were consistent across groups, including among patients with DM.

In the Treating to New Targets (TNT) study, the findings of PROVE IT—TIMI 22 were extended to patients with stable CHD.<sup>21</sup> Intensive statin therapy was associated with a significant 22% reduction in the risk of a first major cardiovascular event relative to less intensive statin therapy. There were no differences in overall

mortality between treatment groups. In a post hoc analysis of the 15% of TNT patients with DM, those who received atorvastatin 80 mg achieved lower LDL-C levels (~77 mg/dL) and had 25% fewer major cardiovascular events than those given the 10-mg dose.<sup>22</sup>

### Consider Niacin or Fibrates, Alone or Combined with Statins, to Raise HDL-C and Lower Triglycerides

The ability of niacin and fibrates to increase HDL-C and lower triglycerides might make them appropriate choices to treat the lipid abnormalities seen in diabetic dyslipidemia. A limited number of studies have evaluated the effects of niacin or fibrates in diabetic patients; results of some studies are presented in **Table 3**.

Niacin monotherapy can increase HDL-C by 15% to 35% and decrease triglycerides by 20% to 50%. It can also beneficially increase low-density lipoprotein particle size.<sup>23</sup> Although some data suggest that niacin may adversely affect glucose control in patients with DM,<sup>24</sup> the extended-release form used at low doses is likely to have little or no negative effect.<sup>25</sup> In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2 (ARBITER 2) trial,<sup>26</sup> a subgroup analysis of 88 patients with insulin resistance (type 2 DM or the metabolic syndrome) showed that the rate of progression of carotid atherosclerosis (intima-media thickness) was reduced in niacin-treated normoglycemic patients but increased in niacin-treated patients with type 2 DM or the metabolic syndrome.<sup>26</sup>

Fibrates can increase HDL-C by 8% to 35% and lower triglycerides by 25% to 50%.<sup>27</sup> However, when a fibrate is used with a statin, fenofibrate is the better choice; it should be used in combination with a statin that is efficacious at the lowest doses in order to minimize the risk of myositis that is sometimes seen with gemfibrozil.<sup>28</sup> In the Helsinki Heart Study,<sup>29</sup> the incidence of CHD was significantly higher among men with diabetes than among men without diabetes. This risk was somewhat although not significantly reduced with gemfibrozil treatment. A subgroup analysis of the Veteran's Affairs HDL Intervention Trial (VA-HIT)<sup>30</sup> showed that in patients with DM, gemfibrozil significantly reduced the risk of CHD death, stroke, or MI by 32%. In patients without DM, gemfibrozil was most effective in those with insulin resistance, reducing the risk of the composite end point by 35%.<sup>30</sup>

In the recently reported Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial,<sup>31</sup> fenofibrate 200 mg/dL failed to significantly reduce the primary outcome of coronary events versus placebo after 5 years; however, the fenofibrate group showed a significant reduction in total cardiovascular events,

**Table 3.** Trials of Niacin and Fibrates—Prospective and Post Hoc Analyses of Diabetic Subgroups

Study	Agents	Objective	N/Patients with DM (or IFG)	Duration of Study	Results
ARBITER 2 <sup>26</sup>	Statin + ER niacin (1000 mg) versus statin + placebo	Effect of treatment on CIMT in patients with CHD and low levels of HDL-C (< 45 mg/dL)	167/46 (85 with metabolic syndrome)	1 yr	CIMT increased significantly in the placebo group ( $0.044 \pm 0.1$ mm; $P < 0.001$ ) but was unchanged in the niacin group ( $0.014 \pm 0.104$ ; $P = 0.23$ ); the difference was not significant
Helsinki Heart Study <sup>29</sup>	Gemfibrozil versus placebo	Effect of treatment on lipid profile and CHD incidence in dyslipidemic patients with type 2 DM and no evidence of CHD	4081/135	5 yr	CHD incidence was 3.4% in gemfibrozil-treated patients with DM versus 10.5% in the placebo group (NS)
VA-HIT <sup>30</sup>	Gemfibrozil 1200 mg/day versus placebo	Effect of treatment on nonfatal MI or CHD death in patients with CHD, average LDL-C, and low HDL-C ( $\leq 40$ mg/dL)	2531/769 (323 with IFG)	5 yr	In patients without DM, gemfibrozil was most effective in those with insulin resistance, lowering risk of composite end point by 35% ( $P = 0.04$ ) In persons with DM, gemfibrozil reduced risk of CHD death, MI, or stroke by 32% ( $P = 0.004$ )
FIELD <sup>31</sup>	Fenofibrate 200 mg/day versus placebo	Effect of fenofibrate on CV events in patients with type 2 DM and average TC, TC:HDL-C ratio of $\geq 4.0$ , or TG 88–443 mg/dL	9795 (all with DM)	5 yr	5.2% of fenofibrate-treated patients had an event versus 5.9% of those on placebo; total CV events were significantly reduced from 13.9% to 12.5% in fenofibrate-treated patients ( $P = 0.035$ )

ARBITER = Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; CHD = coronary heart disease; CIMT = carotid intima-media thickness; CV = cardiovascular; DM = diabetes mellitus; ER = extended-release; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; HDL-C = high-density lipoprotein cholesterol; IFG = impaired fasting glucose; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TG = triglyceride; VA-HIT = Veterans Affairs HDL Intervention Trial.

due primarily to fewer nonfatal MIs and revascularizations. Microvascular complications of DM, such as retinopathy and albuminuria, were also reduced with fenofibrate treatment.<sup>31</sup>

### RECOMMENDATIONS FOR LIPID ASSESSMENT IN PATIENTS WITH DIABETES

Although LDL-C levels are normally calculated using the Friedewald equation, alterations in very-low-density lipoprotein in diabetic patients could make such calculations unreliable. Therefore, because a precise quantification of LDL-C is critical, it is recommended that LDL-C be measured directly in patients in whom triglyceride levels are likely to range from 200 to 400 mg/dL. A direct cholesterol assay, currently available in most laboratories, is the preferred method to obtain an accurate lipid profile in hypertriglyceridemic diabetic patients. Lipid levels in adult patients should be measured at least once annually, or more often as necessary to monitor achievement of lipid goals.<sup>32</sup> If the initial measurement yields values denoting a patient at low risk, the lipid profile can be repeated after 2 years.

Non-HDL-C (total cholesterol minus HDL-C) in-

cludes the cholesterol in all the atherogenic lipoproteins. It has therefore been proposed as an accurate predictor of CVD risk in patients with diabetic dyslipidemia,<sup>33</sup> although some experts claim that it provides less information than the total cholesterol:HDL-C ratio.<sup>34</sup> A recent study found that apolipoprotein B, a measure of the total number of atherogenic particles, predicted cardiovascular risk more accurately than non-HDL-C or LDL-C.<sup>35</sup> However, since lowering LDL-C remains the mainstay of treatment for dyslipidemia,<sup>7</sup> there is no justification at this time for replacing it as a risk predictor. In diabetic patients with hypertriglyceridemia or those who do not reach their lipid targets with intensive LDL-C-lowering treatment, non-HDL-C may be considered a secondary target of therapy. In this case, the goal of therapy would be to achieve a non-HDL-C level 30 mg/dL higher than the LDL-C goal.<sup>7</sup>

### LIPID-LOWERING TARGETS IN PATIENTS WITH DIABETES

Practice guidelines, such as those prepared by the American College of Physicians (ACP),<sup>36</sup> support broad use of lipid-lowering therapy in all patients with DM for secondary prevention, and in patients with DM and other cardiovascular risk factors for primary prevention.

**Table 4.** Current Guidelines for Treatment of Patients with Diabetic Dyslipidemia

Serum Cholesterol Level	Treatment Recommendations
LDL-C $\geq$ 130 mg/dL	Initiate TLC in all persons (NCEP, ADA) Many persons with type 1 or type 2 DM will require LDL-C-lowering drugs (statins are usually first choice) (NCEP, ADA) LDL-C goal: $\leq$ 100 mg/dL (NCEP, ADA) If triglycerides $\geq$ 200 mg/dL: Consider treatment with fibrate or low-dose (< 3 g/day [2 g/day per ADA]) nicotinic acid (either as alternative to or in combination with LDL-C-lowering drug) to achieve non-HDL-C goal of < 130 mg/dL (NCEP) Lower triglycerides to < 150 mg/dL (ADA) Raise HDL-C to > 40 mg/dL in men, > 50 mg/dL in women (ADA) If triglycerides are high, HDL-C is low, or patient has CVD but LDL-C is near normal, use fibrate therapy (ADA) Intensively treat nonlipid risk factors (hypertension, cigarette smoking, hyperglycemia) (NCEP, ADA)
TC $\geq$ 135 mg/dL (or patient > 40 yr of age)	Lower LDL-C to 100 mg/dL (or $\sim$ 30%), regardless of baseline LDL-C (ADA)
Baseline LDL-C of 100–129 mg/dL	Initiate TLC in all persons (NCEP) Intensively treat nonlipid risk factors (NCEP) If triglycerides $\geq$ 200 mg/dL, consider treatment with fibrate or low-dose (< 3 g/day [2 g/day per ADA]) nicotinic acid (either as alternative to or in combination with LDL-C-lowering drug) to achieve goal for non-HDL-C of < 130 mg/dL (NCEP)
On-treatment LDL-C of 100–129 mg/dL	Intensify TLC in all persons (NCEP) Intensively treat nonlipid risk factors (NCEP) If triglycerides $\geq$ 200 mg/dL, consider adding fibrate or low-dose nicotinic acid (< 3 g/day [2 g/day per ADA]) to statin therapy to achieve non-HDL-C goal < 130 mg/dL (NCEP)
Baseline LDL-C < 100 mg/dL	Initiate TLC in all persons to reduce overall risk (NCEP) Intensively treat nonlipid risk factors (NCEP) If triglycerides $\geq$ 200 mg/dL, consider using a fibrate or low-dose nicotinic acid (< 3 g/day [2 g/day per ADA]) to achieve non-HDL-C goal < 130 mg/dL (NCEP)
In all patients with DM and established CVD or with DM and older age and/or multiple risk factors, consider an LDL-C target of $\leq$ 70 mg/dL (NCEP)	

Data from Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): final report,<sup>7</sup> Haffner,<sup>32</sup> and Grundy et al.<sup>38</sup>

ADA = American Diabetes Association; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TLC = therapeutic lifestyle changes.

Based on a meta-analysis of 6 primary prevention trials, the ACP practice guidelines suggest that the benefit of statin therapy is similar in all persons with DM, regardless of their baseline cholesterol level.<sup>37</sup>

For patients with DM and established CVD, current guidelines from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III recommend that clinicians consider an LDL-C goal of 70 mg/dL or less<sup>38</sup> (Table 4). Most patients with DM without CVD should be treated with the same intensity as patients with established CVD (ie, consider drug therapy when LDL-C is  $\geq$  100 mg/dL to reach a goal of < 100 mg/dL). A small proportion of patients with DM will have a 1-year CHD risk below 20%. For these patients, lipid-lowering drugs should be instituted when LDL-C levels are 130 mg/dL or higher, provided the patient adheres to strict dietary and exercise recommendations.<sup>7,38</sup>

The American Diabetes Association (ADA) advocates

similarly stringent LDL-C goals for patients with DM.<sup>32</sup> ADA guidelines recommend that adults with DM reduce their LDL-C to 100 mg/dL or lower, or by 30% if total cholesterol is 135 mg/dL or higher. The ADA also suggests that combination therapy with a statin and fibrate or nicotinic acid may be necessary in some cases.<sup>32</sup> Since the available clinical trial data on diabetic patients are derived predominantly from persons aged 40 years or older, it might be prudent to start therapy at age 40, except in very high-risk diabetic patients, such as those with preexisting CVD or other risk factors (eg, smoking, hypertension, microalbuminuria).

Overall, statins appear to be safe and well tolerated in the majority of patients. In providing guidelines on monitoring the risk of adverse events with these agents, the clinical advisory issued by the American College of Cardiology, American Heart Association, and the National Heart, Lung, and Blood Institute noted that elevations in liver enzymes tend to be dose related.<sup>39</sup>

Therefore, it may be prudent to use statins that provide maximum efficacy at low doses in order to minimize the risk of adverse events.

## SUMMARY

Statins remain the gold standard for reducing LDL-C in patients with DM. A number of large primary and secondary prevention clinical trials have provided strong evidence of their benefits in reducing CVD end points in a wide variety of patient populations, including those with type 2 DM. Aggressive LDL-C reduction with statins remains a cornerstone of treatment in diabetic patients with established CVD or at high risk for CVD, as recommended by the practice guidelines of the NCEP and the ADA. In keeping with the spirit of these guidelines, it is prudent to use statin therapy that is potent enough to achieve target LDL-C levels while avoiding the very high doses that have elicited safety concerns. Niacin and fibrates are possible choices in patients who require additional triglyceride lowering or HDL-C raising after the LDL-C goal has been met. **HP**

## REFERENCES

1. National Institutes of Health, National Heart, Lung, and Blood Institute. Fact book fiscal year 2005. Available at [www.nhlbi.nih.gov/about/05factbk.pdf](http://www.nhlbi.nih.gov/about/05factbk.pdf). Accessed 13 Jun 2006.
2. Fox CS, Coady S, Sorlie PD, et al. Trends in cardiovascular complications of diabetes. *JAMA* 2004;292:2495–9.
3. Miettinen H, Lehto S, Salomaa V, et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care* 1998;21:69–75.
4. Mokdad AH, Serdula MK, Dietz WH, et al. The continuing epidemic of obesity in the United States [letter]. *JAMA* 2000;284:1650–1.
5. Mokdad AH, Bowman BA, Ford ES, et al. The continuing epidemics of obesity and diabetes in the United States. *JAMA* 2001;286:1195–200.
6. Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 1998;316:823–8.
7. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): final report. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation* 2002;106:3143–421.
8. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group [published erratum appears in *Lancet* 1999;354:602]. *Lancet* 1998;352:837–53.
9. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383–93.
10. Haffner SM, Lehto S, Ronnema T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229–34.
11. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 2000;102:1014–9.
12. Pyorala K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) [published erratum appears in *Diabetes Care* 1997;20:1048]. *Diabetes Care* 1997;20:614–20.
13. Goldberg RB, Mellies MJ, Sacks FM, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. *Circulation* 1998;98:2513–9.
14. Haffner SM, Alexander CM, Cook TJ, et al. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1999;159:2661–7.
15. Keech A, Colquhoun D, Best J, et al. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. LIPID Study Group. *Diabetes Care* 2003;26:2713–21.
16. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Heart Protection Study Collaborative Group. *Lancet* 2003;361:2005–16.
17. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. ASCOT Investigators. *Lancet* 2003;361:1149–58.
18. Killestein J. ASCOT-LLA: questions about the benefits of atorvastatin [letter]. *Lancet* 2003;361:1986–7.
19. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. CARDS Investigators. *Lancet* 2004;364:685–96.
20. Cannon CP, Braunwald E, McCabe CH, et al. Intensive

- versus moderate lipid lowering with statins after acute coronary syndromes [published erratum appears in *N Engl J Med* 2006;354:778]. Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 Investigators. *N Engl J Med* 2004;350:1495–504.
21. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. Treating to New Targets (TNT) Investigators. *N Engl J Med* 2005;352:1425–35.
  22. Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 2006;29:1220–6.
  23. Miller M. Niacin as a component of combination therapy for dyslipidemia. *Mayo Clin Proc* 2003;78:735–42.
  24. Garg A, Grundy SM. Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. *JAMA* 1990;264:723–6.
  25. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Diabetes Multicenter Research Group. *Arch Intern Med* 2002;162:1568–76.
  26. Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins [published errata appear in *Circulation* 2004;110:3615 and 2005;111:e446]. *Circulation* 2004;110:3512–7.
  27. Fruchart JC, Staels B, Duriez P. PPARs, metabolic disease and atherosclerosis. *Pharmacol Res* 2001;44:345–52.
  28. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* 2005;95:120–2.
  29. Koskinen P, Manttari M, Manninen V, et al. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 1992;15:820–5.
  30. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med* 2002;162:2597–604.
  31. Keech A, Simes RJ, Barter P. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. FIELD study investigators. *Lancet* 2005;366:1849–61.
  32. Haffner SM. Dyslipidemia management in adults with diabetes. American Diabetes Association. *Diabetes Care* 2004;27 Suppl 1:S68–71.
  33. Lu W, Resnick HE, Jablonski KA, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. *Diabetes Care* 2003;26:16–23.
  34. Holman RR, Coleman RL, Shine BS, Stevens RJ. Non-HDL cholesterol is less informative than the total-to-HDL cholesterol ratio in predicting cardiovascular risk in type 2 diabetes. *Diabetes Care* 2005;28:1796–7.
  35. Pischon T, Girman CJ, Sacks FM, et al. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation* 2005;112:3375–83.
  36. Snow V, Aronson MD, Hornbake ER, et al. Lipid control in the management of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Clinical Efficacy Assessment Subcommittee of the American College of Physicians. *Ann Intern Med* 2004;140:644–9.
  37. Vijan S, Hayward RA. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. American College of Physicians. *Ann Intern Med* 2004;140:650–8.
  38. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines [published erratum appears in *Circulation* 2004;110:763]. National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, American Heart Association. *Circulation* 2004;110:227–39.
  39. Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. American College of Cardiology, American Heart Association, National Heart, Lung and Blood Institute. *J Am Coll Cardiol* 2002;40:567–72.

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