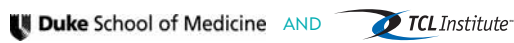


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# DISSECTING DIABETIC DYSLIPIDEMIA

## Understanding Causes and Implementing Solutions

### DISSECTING DIABETIC DYSLIPIDEMIA: UNDERSTANDING CAUSES AND IMPLEMENTING SOLUTIONS

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**RELEASE DATE:** March 20, 2009  
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#### STATEMENT OF NEED

The American Diabetes Association (ADA) estimated that over 21.5 million Americans have diabetes. The Centers for Disease Control and Prevention report that from 70% to 97% of people with diabetes have dyslipidemia, a term encompassing several lipid disorders including: elevated low-density lipoprotein cholesterol (LDL-C), elevated serum triglycerides, and diminished high-density lipoprotein cholesterol (HDL-C).

Management of dyslipidemia is currently the predominant topic of discussion and research on cardiovascular issues in diabetes care,<sup>1</sup> and many ongoing studies are investigating combination lipid control strategies and their effects on cardiovascular outcomes in diabetic patients.

Despite the fact that dyslipidemia is known to be a significant risk factor for the development of macrovascular diabetic complications, awareness and proper treatment of dyslipidemia are lacking. A recent ADA/American College of Cardiology survey of individuals with diabetes reported that 60% of individuals with diabetes do not believe they are at risk for cholesterol problems. Only 8% of individuals with diabetes reported that their health care provider ever discussed lowering cholesterol.<sup>2</sup>

This monograph will provide up-to-date information on the diagnosis and treatment of dyslipidemia in patients with type 2 diabetes and outline strategies for educating patients with dyslipidemia on the importance of lipid control.

#### TARGET AUDIENCE

This activity is designed for primary care physicians, physician assistants, nurses, pharmacists, and nurse practitioners who treat dyslipidemia in patients with diabetes.

#### LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Recognize the impact of dyslipidemia on morbidity and mortality in patients with diabetes
- Utilize effective strategies for educating patients on the importance of lipid level management in their battle with cardiovascular disease
- Review the role of pharmacotherapy in helping patients with diabetes meet their LDL-C, HDL-C, and triglyceride targets
- Implement strategies for improving communication between patients with diabetic dyslipidemia and health care providers regarding the management of their disease state
- Apply lifestyle modification and pharmacological techniques to help patients reach their lipid level targets and goals

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<sup>1</sup> Buse JB, Rosenstock J. Prevention of cardiovascular outcomes in type 2 diabetes mellitus: trials on the horizon. *Endocrinol Metab Clin North Am*. 2005;34(1):221-235.

<sup>2</sup> Awareness of diabetes-heart disease link lacking. American Diabetes Association Web site. <http://www.diabetes.org/for-media/general-press-releases/2002-press-releases/02-20-02.jsp>. Published February 19, 2002. Accessed December 29, 2008.

# DISSECTING DIABETIC DYSLIPIDEMIA

## Understanding Causes and Implementing Solutions

### TREATMENT OF DYSLIPIDEMIA IN PATIENTS WITH DIABETES

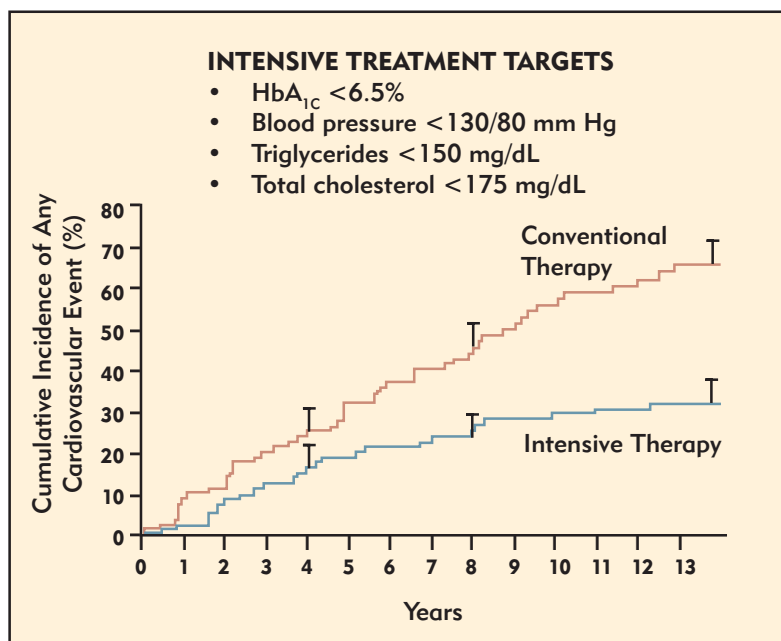
#### Introduction

Type 2 diabetes presently accounts for 6% of total global mortality, with approximately 65% of diabetes-related deaths resulting from heart disease or stroke among people aged 65 years or older.<sup>1,2</sup> An integral relationship exists between type 2 diabetes, dyslipidemia, and hypertension. This relationship is evident in the fact that the prevalence of insulin resistance is 58% in people with hypertension, 88% in people with diminished high-density lipoprotein cholesterol levels (HDL-C; ie, <40 mg/dL), and 95% in people having both hypertension and low HDL-C levels or a cluster of other such metabolic disorders.<sup>3</sup> The risk of cardiovascular disease (CVD) in patients having both hypertension and type 2 diabetes is almost twice that of patients having hypertension alone.<sup>4</sup> Additionally, the Strong Heart Study reports that cardiovascular complications associated with elevated low-density lipoprotein cholesterol levels (LDL-C; ie, >100 mg/dL) are more frequent in individuals having concurrent insulin resistance, or type 2 diabetes, than in individuals who have neither condition.<sup>5</sup> As a consequence of this relationship, the risk of mortality due to cardiovascular complications is 2 to 4 times greater among people having diabetes than among those who do not.<sup>2</sup> This relationship can be expected to have a growing impact on health care since the World Health Organization projects that the worldwide prevalence of type 2 diabetes, which is now approximately 180 million, will double by 2030.<sup>6,7</sup> The majority of new cases will occur in people aged 45 to 64 years.

Although the pathophysiological relationship between hyperglycemia, hypertension, and dyslipidemia has not yet been fully elucidated, the American Diabetes Association (ADA) presently recommends a comprehensive treatment strategy to reduce cardiovascular risk by concurrently addressing all 3 of these dysfunctions.<sup>8</sup> The ADA has established evidence-based treatment targets for hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), blood pressure, and serum cholesterol levels in patients with type 2 diabetes.<sup>8</sup> Recent controversy arising from the early stoppage of the glycemic control arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD)

trial has raised questions about the value of including HbA<sub>1c</sub> reduction in a cardiovascular risk reduction strategy for patients with type 2 diabetes. The ACCORD trial targeted an HbA<sub>1c</sub> goal of <6.0% in patients with type 2 diabetes who had a high level of cardiovascular risk, and the trial was stopped when it was found that the intensive treatment group had experienced 14 deaths per 1000, compared to 11 deaths per 1000 in the standard treatment group.<sup>9</sup> However it is important to note that the risk of death at baseline for the ACCORD study population was estimated at 50 per 1000. Subsequent publication of results from the ADVANCE and Veterans Affairs Diabetes Trial (VADT) have confirmed that intensive glycemic

Figure 1. Steno-2 Long-Term Follow-up Study



A total of 160 patients were treated for 7.8 years and 130 patients were followed-up for an additional 5.5 years (13.3 years total). Intensive treatment reduced the risk of cardiovascular death by 29% ( $P<0.001$ ). Reprinted with permission from Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008;358(6):580-591. Copyright © 2008 Massachusetts Medical Society. All rights reserved.<sup>12</sup>

treatment targets (ie, HbA<sub>1c</sub> <6.5%) in subjects with elevated cardiovascular risk do not augment the reduction of cardiovascular risk in high-risk populations.<sup>10,11</sup> As shown in **Figure 1** however, the Steno-2 study demonstrates that a comprehensive treatment strategy concurrently targeting HbA<sub>1c</sub>, blood pressure, and serum cholesterol yields significant, long-term cardiovascular risk reduction in patients with type 2 diabetes who do not have a prior history of cardiovascular events.<sup>12</sup>

# DISSECTING DIABETIC DYSLIPIDEMIA

## Understanding Causes and Implementing Solutions

### HOW DOES CHOLESTEROL ENTER THE CIRCULATION?

Circulating levels of cholesterol represent a sum total of lipids originating from dietary intake and from lipid-protein complexes that are synthesized *de novo* in the liver.<sup>13</sup> Cholesterol is transported through the circulation in the form of cholesterol esters associated with lipoproteins. Components of the overall serum lipid profile include chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL-C, HDL-C, triacylglycerol (TG), and free fatty acid (FFA).

**Chylomicrons**—Chylomicrons are assembled in the intestinal mucosa from dietary cholesterol and TG.<sup>13</sup> Chylomicrons facilitate the transport of these hydrophobic lipids through the aqueous environment of the circulatory system. Chylomicrons deliver dietary TGs to adipose and muscle tissues, and dietary cholesterol to the liver. They are composed primarily of TG combined with a number of different apoproteins including apolipoprotein A (apoA)-I, -II, and -IV; apolipoprotein B (apoB)-48; and apolipoprotein C (apoC)-I, -II, and -III. The enzyme lipoprotein lipase, which is found on epithelial cells in the capillaries of adipose and muscle tissues, is activated by apoC-II and releases FFAs from chylomicrons. After the FFAs are absorbed by tissues, much of the remaining apoA, apoC, and phospholipid molecules in the chylomicron remnants are transferred to HDL-C particles. The chylomicron remnants then go on to deliver cholesterol to the liver through an interaction with specific receptors in the liver.

**VLDL**—VLDL particles are formed in the liver and released into the circulation where they carry TGs, and to a lesser extent cholesterol, to nonhepatic tissues.<sup>13</sup> VLDL particles can contain both dietary cholesterol and newly synthesized endogenous cholesterol. VLDL particles also contain apoB-100; apoC-I, -II, and -III; and apolipoprotein E (apoE). VLDL particles release FFAs into muscle and adipose tissue through a lipoprotein lipase-depen-

dent mechanism similar to chylomicrons. This process results in VLDL remnants called IDL.

**IDL-C**—IDL particles are converted to LDL-C by the removal of additional TG molecules; however IDL may be endocytosed by the liver through an interaction of the hepatic LDL-C receptor with apoB-100 and apoE molecules on the IDL particle.<sup>13</sup>

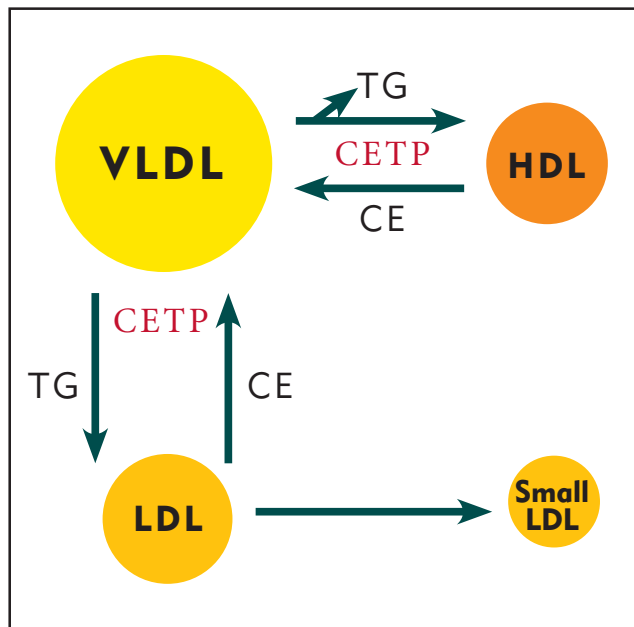
**LDL-C**—LDL-C particles are the primary transporters of cholesterol to the tissues, carrying both dietary cholesterol and endogenous cholesterol synthesized by the liver.<sup>13</sup> ApoB-100 is the only apoprotein contained in LDL-C particles, and it provides the specific interaction with LDL-C receptors that triggers the transport of LDL-C particles into the tissues via LDL-C receptor-mediated

endocytosis. LDL-C is found in the circulation as either large, buoyant particles or small dense particles, which may be more atherogenic than the larger particles.<sup>14</sup>

**HDL-C**—HDL-C particles are synthesized in the liver and small intestine, then enter the circulation where their overall function is to scavenge and dispose of excess cholesterol from various sources.<sup>13</sup> Another important function of HDL-C particles is to serve as a source of apoA-I/-II and apoE, which determine the specificity of certain interactions between HDL-C and macrophages, liver, or other lipoprotein particles. HDL-C can incor-

porate free cholesterol from VLDL remnants or extract cholesterol from cell surfaces. HDL-C particles also can be endocytosed by macrophages, through an apoA-I interaction, where they incorporate cholesterol and apoE before reentering the circulation. As shown in **Figure 2**, cholesterol can then be transferred from HDL-C to VLDL or LDL-C through the action of cholesterol ester transfer protein (CETP), which is associated with HDL-C.<sup>15,16</sup> HDL-C returns cholesterol to the liver where it binds to scavenger receptor class B type 1 and delivers cholesterol ester to the hepatocytes. In this way, excess cholesterol can be excreted either as free cholesterol or as bile salts synthesized by the liver.

**Figure 2. Interactions of Circulating Lipoprotein Particles**



Reprinted with permission from Goldberg IJ. Clinical review 124: Diabetic dyslipidemia: causes and consequences. *J Clin Endocrinol Metab.* 2001;86(3):965-971.<sup>16</sup>

# DISSECTING DIABETIC DYSLIPIDEMIA

## Understanding Causes and Implementing Solutions

### THE RELATIONSHIP BETWEEN DIABETES AND SERUM CHOLESTEROL

Diabetes and cholesterol metabolism intersect at a number of points. For instance, synthesis of lipoprotein lipase is regulated, in part, by insulin. Insulin and thyroid hormone also promote the interaction of LDL-C with LDL-C receptor.<sup>13</sup> When cholesterol is not used or excreted normally by the body, high intracellular cholesterol levels have a negative-feedback effect on synthesis of LDL-C receptor by the liver. Cellular uptake of LDL-C, due to down-regulation of the LDL-C receptor, results in higher circulating LDL-C levels. The excess cholesterol carried by the LDL-C particles is deposited in skin and tendons, but more importantly, in arterial walls. As this deposition continues, plaque formation builds and atherosclerosis develops. In patients with type 2 diabetes, dyslipidemia is most often characterized by elevated triglycerides (ie, >150 mg/dL) and diminished levels of HDL-C (ie, <40 mg/dL).<sup>17</sup> **Table 1** summarizes characteristics of dyslipidemia that are associated with diabetes.<sup>18</sup>

Although markedly elevated LDL-C levels are not a defining feature of type 2 diabetes, LDL-C in patients with type 2 diabetes tends to contain a higher proportion of atherogenic small, dense particles rather than larger, more buoyant LDL-C particles.<sup>14</sup> This observation is significant in terms of cardiovascular risk because the smaller, denser particles have the capability of entering endothelial spaces, binding endothelial proteoglycans, and undergoing oxidation or glycation, all of which contribute to the progression of atherosclerosis. Thus, in patients with type 2 diabetes, the concentration and size of LDL-C particles may be more revealing than the total unfractionated LDL-

**Table 1. Characteristics of Diabetic Dyslipidemia**

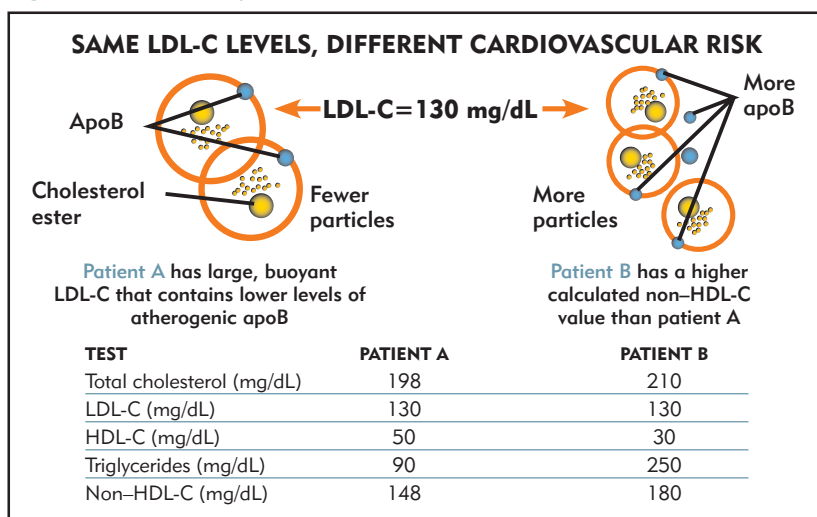
<b>Diminished HDL-C</b>
<b>Elevated non-HDL-C</b>
<b>Elevated triglycerides</b>
<b>Elevated apoB</b>
<b>Elevated apoC-III</b>
<b>Diminished apoA-I</b>
<b>Small, dense LDL-C particles</b>

Adapted from Fruchart J-C, Sacks FM, Hermans MP, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in dyslipidaemic patients. *Diab Vasc Dis Res.* 2008;5(4):319-335.<sup>18</sup>

C measurement in determining cardiovascular risk, especially in patients with hypertriglyceridemia. Since apoB is only found in LDL-C, and each LDL-C particle contains only 1 apoB molecule, measuring apoB levels provides a good estimate of LDL-C particle concentration (**Figure 3**).<sup>19</sup> A recent consensus statement issued jointly by the ADA and the American College of Cardiology suggests that highest-risk patients (ie, those with known CVD or diabetes plus 1 or more additional major risk factors for CVD) should be treated to an LDL-C goal of <70 mg/dL.<sup>14</sup> The consensus panel further recommends that high-risk patients (ie, those without diabetes or CVD but with 2 or more other major CVD risk factors, and those with diabetes but no other major CVD risk factors) should be treated to an LDL-C goal of <100 mg/dL.

Evidence suggests not only an interaction between the pathological mechanisms of dyslipidemia and established diabetes, but also a possible relationship between dyslipidemia and the development of new-onset diabetes. A recent report following more than 14,000 hypertensive patients who were at risk of developing diabetes found that in addition to baseline fasting plasma glucose and body mass index (BMI), high serum triglyceride levels and high systolic blood pressure were also significant predictors of developing new-onset diabetes.<sup>20</sup> It also was noted that a high HDL-C level was among the protective factors against new-onset diabetes. Interestingly, treatment of hypertension with amlodipine

**Figure 3. Relationship of LDL-C Particle Size and Cardiovascular Risk**



In the example shown above, the lipid profile of patient B is associated with a 19% higher risk in men and an 11% higher risk in women of having a fatal cardiac event due to a more atherogenic clinical profile associated with apoB. Data adapted from Unger J, ed. *Diabetes Management in Primary Care*. Philadelphia, PA: Lippincott, Williams and Wilkins; 2007:504-617.<sup>19</sup> Image courtesy of Unger J.

# DISSECTING DIABETIC DYSLIPIDEMIA

## Understanding Causes and Implementing Solutions

**Table 2. NCEP ATP-III Guidelines for Cholesterol-Lowering Therapy<sup>21,22</sup>**

Risk Category	LDL-C Goal	LDL-C Level at Which to Initiate Therapeutic Lifestyle Changes	LDL-C Level at Which to Consider Drug Therapy
CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL drug optional)*
2+ risk factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10%-20% ≥130 mg/dL ..... 10-year risk <10% ≥160 mg/dL
0-1 risk factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL; LDL-C-lowering drug optional)

\* Some authorities recommend use of LDL-C-lowering drugs in this category if an LDL-C <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C (eg, nicotinic acid or fibrate). Clinical judgment also may call for deferring drug therapy in this subcategory.

† Almost all people with a 0-1 risk factor have a 10-year risk of <10%; thus, 10-year risk assessment in people with a 0-1 risk factor is not necessary.

± perindopril was protective against new-onset diabetes compared with atenolol ± thiazide treatment. A more complete understanding of the physiological relationships between hyperglycemia, hypertension, and dyslipidemia represented in the observations described above may lead to new therapeutic approaches for reducing cardiovascular risk in diabetes, and perhaps development of diabetes.

**Table 3. Priorities for Treating Dyslipidemia in Patients With Diabetes**

<b>1. LDL-C lowering</b>	Lifestyle modifications <b>PREFERRED:</b> Statins <b>OTHER OPTIONS:</b> Bile acid sequestrant, fibrate, niacin, cholesterol absorption inhibitor
<b>2. HDL-C raising</b>	Lifestyle modifications Niacin or fibrate
<b>3. Triglyceride lowering</b>	Lifestyle modifications Intensify glycemic control Fibrate and/or niacin High-dose statin (in the presence of high LDL-C)
<b>4. Combined dyslipidemia</b>	<b>FIRST CHOICE:</b> Improved glycemic control plus high-dose statin <b>SECOND CHOICE:</b> Improved glycemic control plus statin plus fibrate <b>THIRD CHOICE:</b> Improved glycemic control plus statin plus niacin

Data from American Diabetes Association. Standards of medical care in diabetes—2009. *Diabetes Care*. 2009;32(suppl 1):S13-S61.<sup>8</sup> and American Diabetes Association. Dyslipidemia management in adults with diabetes. *Diabetes Care*. 2004;27(suppl 1):S68-S71.<sup>17</sup>

### RECOMMENDATIONS FOR TREATING DYSLIPIDEMIA IN PATIENTS WITH DIABETES

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) has issued guidelines for treatment of dyslipidemia in patients who are at various levels of cardiovascular risk (Table 2).<sup>21,22</sup> The primary target of these guidelines is LDL-C level, but the guidelines also recommend that non-HDL-C level be considered as a secondary target of lipid-lowering therapies in people with elevated triglycerides (ie, ≥200 mg/dL). The non-HDL-C measure represents the total of LDL-C, VLDL, and the catabolic byproduct of VLDL, IDL, which are all contributors to atherosclerosis.<sup>14,21</sup> The target level for non-HDL-C is set at 30 mg/dL higher than the LDL-C target. The decision to treat is determined by considering the patients' LDL-C level within the context of their overall cardiovascular risk. For instance, an LDL-C level of 130 mg/dL should trigger pharmacological treatment in a high-risk patient, lifestyle modification in a moderate-risk patient, and would not necessarily be treated in a low-risk patient.

When treatment is warranted, the ADA provides specific recommendations for treating the different forms of dyslipidemia that are commonly found in patients with diabetes.<sup>8,17</sup> These recommendations are shown in Table 3. For most patients, the first treatment step employs therapeutic lifestyle change. Lifestyle modification emphasizes the reduction of saturated fat, *trans* fat, and cholesterol intake; weight loss (if indicated); increased physical activity; and smoking cessation. The guidelines also recommend that high-risk patients with elevated triglycerides or low HDL-C consider combining LDL-C-lowering therapy with fibrate or niacin.

# DISSECTING DIABETIC DYSLIPIDEMIA

## Understanding Causes and Implementing Solutions

### TREATING HIGH LDL-C LEVELS IN PATIENTS WITH DIABETES

Given the high rate of cardiovascular deaths associated with type 2 diabetes, cardiovascular risk reduction is an important goal in any diabetes regimen. For patients with diabetes who already have an elevated cardiovascular risk, evidence has not supported a strategy of intensive glucose control to reduce cardiovascular risk. These findings suggest that providers should emphasize cholesterol and blood pressure control to improve cardiovascular risk reduction in their patients with diabetes. Numerous clinical trials have demonstrated significant effects of statin therapy on cardiovascular risk in subjects with coronary heart disease (CHD). Recent meta-analyses conducted with many of these trials confirm that lipid-lowering treatment, especially with statins, significantly reduces cardiovascular risk in both diabetic and non-diabetic populations.<sup>23,24</sup> Many of these statin trials that pertain specifically to diabetic populations are listed in **Table 4**.<sup>25-29</sup> The overall reduction of cardiovascular outcomes (CHD death and nonfatal myocardial infarction [MI]) is most apparent in diabetic subjects with high baseline cardiovascular risk. Since vascular inflammation has an important role in atherosclerosis,<sup>30</sup> it is likely that the higher incidence of cardiovascular events in diabetes involves an increase in the vascular inflammatory process.<sup>31</sup> The inflammatory protein high-sensitivity C-reactive protein (hs-CRP) may be useful as a treatment target for assessing cardiovascular risk reduction with statin therapy in patients with diabetes because elevated hs-CRP levels are closely associated with cardiovascular

events in patients with diabetes.<sup>32</sup> Patients with diabetes whose hs-CRP level was above 3.0 mg/L were reported to have a 1.6-fold higher mortality rate than patients whose hs-CRP level was below 3.0 mg/L.<sup>33</sup> As a caveat, patients with persistently, markedly elevated hs-CRP levels (ie,  $\geq 10$  mg/L) should be evaluated for other, noncardiovascular causes of the elevation like cancer or autoimmune disease.

The benefits of statin therapy in people who have diabetes and moderate risk of cardiovascular events are also significant. Results from a number of clinical trials of statin treatment for reduction in risk of major CVD end points (CHD death/nonfatal MI) are listed in **Table 4** for comparison.<sup>25-29</sup> Using results from these and other clinical trials, a log-linear relationship between LDL-C and cardiovascular risk has been derived in which every 30-mg/dL reduction in LDL-C correlates with a relative CHD risk reduction of about 30%.<sup>21</sup> This relationship implies that patients having equally high cardiovascular risk due either to elevated LDL-C, or low LDL-C plus other risk factors, can expect to obtain the same absolute risk reduction after achieving the same absolute amount of LDL-C reduction.

Statin are currently widely used and are the best-characterized cholesterol-lowering, pharmacological agent. Statins have consistently been reported to reduce cardiovascular risk in clinical trials studying patients with diabetes and dyslipidemia.<sup>8</sup> These studies were of differing lengths (3.3-5.4 years) and used somewhat different outcomes, but all of them reported rates of CVD death and nonfatal MI.<sup>8</sup>

**Table 4. Reduction of Cardiovascular Risk in Diabetes Patients With Statins**

Trial	Diabetes Patients	Total Patients	Medication (mg/day)	CHD Risk
CARDS <sup>25</sup>	2838	2838	Atorvastatin 10 mg	-37% ( $P=0.001$ )*
HPS <sup>26†</sup>	5963	7150	Simvastatin 40 mg	-27% ( $P<0.0001$ )*
ASCOT <sup>27</sup>	2532	10,305	Atorvastatin 10 mg	-16% (not significant)
TNT <sup>28</sup>	1501	1501	Atorvastatin 80 mg vs 10 mg	-25% ( $P=0.026$ )‡
AFCAPS/ TexCAPS <sup>29</sup>	155	6605	Lovastatin 20-40 mg	-37% ( $P<0.001$ )*

\* Relative risk vs placebo in patients with type 2 diabetes.

† Type 1 and type 2 diabetes.

‡ Relative risk 80 mg vs 10 mg in patients with type 2 diabetes.

# DISSECTING DIABETIC DYSLIPIDEMIA

## Understanding Causes and Implementing Solutions

### LOWERING LDL-C LEVELS WITH BILE ACID SEQUESTRANTS

An alternative mechanism for lowering LDL-C levels is through bile acid sequestrants, which have been shown to decrease LDL-C when used either as monotherapy or in combination with other agents.<sup>34</sup> Bile acid sequestrants bind to bile acids in the intestine, which reduces the absorption of dietary cholesterol and causes significant reductions in LDL-C levels. Since sequestered bile acids are subsequently excreted, the use of bile acid sequestrants also leads to increased synthesis of new bile acids by the liver to replenish the diminished supply.<sup>35</sup> This action further contributes to total cholesterol reduction because cholesterol is a required component of new bile acid synthesis. The most commonly used bile acid sequestrants, colestipol, colesevelam, and colestyramine, have been shown to reduce LDL-C, increase HDL-C, and reduce the risk of CHD.<sup>21,35</sup> When used in patients with diabetes, bile acid sequestrants have the additional benefit of lowering blood glucose levels through a mechanism that is not yet fully understood. In a recent trial, patients with type 2 diabetes were treated for 12 weeks with colesevelam, in addition to their usual oral anti-diabetic medication. Relative to placebo, colesevelam significantly reduced HbA<sub>1c</sub> and postprandial glucose levels while significantly reducing LDL-C levels, LDL-C particle concentration, and apoB.<sup>36</sup> Reduction of HbA<sub>1c</sub>

in patients with type 2 diabetes has also been noted with use of other bile acid sequestrants, including colestimide and cholestyramine.<sup>34</sup>

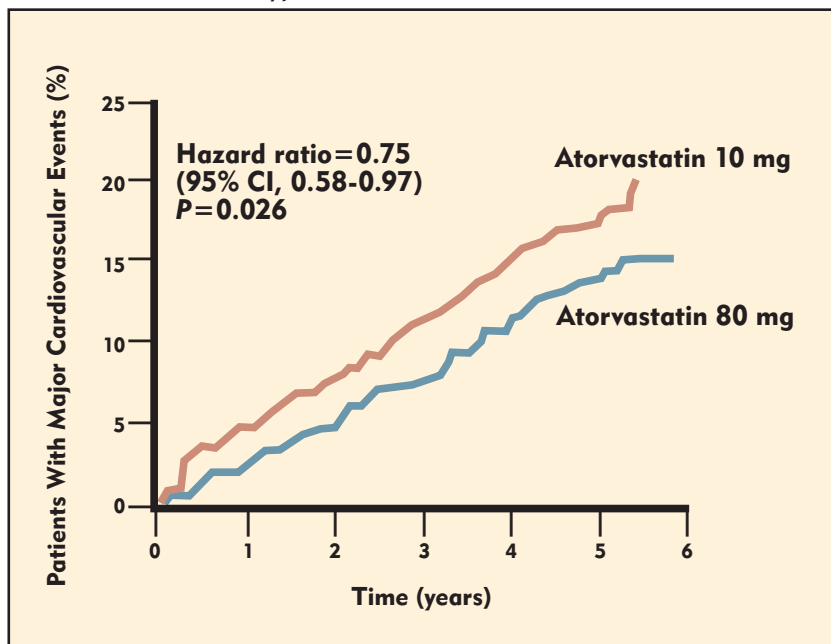
### MINIMIZING CARDIOVASCULAR RISK DUE TO DYSLIPIDEMIA IN PATIENTS WITH DIABETES

Increasingly greater reductions in circulating levels of LDL-C appear to yield additional cardiovascular risk reduction in patients with diabetes.<sup>21</sup> As shown in **Figure 4**, a recent study investigating intensive LDL-C lowering (mean LDL-C, 77 mg/dL vs 99 mg/dL) in patients with type 2 diabetes reported an additional 25% reduction in major cardiovascular events in participants who achieved the more intensive LDL-C goal.<sup>32</sup> The need for new approaches to reducing cardiovascular risk is evidenced by the substantial number of people with diabetes who remained at high cardiovascular risk despite having effectively lowered their LDL-C levels. Additional risk reduction may be achieved by targeting HDL-C and possibly triglycerides.<sup>18</sup>

### TREATING HIGH TRIGLYCERIDES IN DIABETES

Serum triglycerides are a surrogate measure used to estimate VLDL particles in the serum. Since larger VLDL particles are not able to penetrate the endothelium and enter vascular walls, individuals with benign hypertriglyceridemias characterized by large VLDL particles are not necessarily at increased cardiovascular risk.<sup>14</sup> Specifically lowering triglycerides in patients with diabetes has not yet been shown to independently lower cardiovascular event rates. Triglycerides, however, are a marker for increased risk of cardiovascular events. A recent analysis of the triglyceride levels of participants in a lipid-lowering trial comparing 2 different statins in patients who had experienced an acute coronary syndrome (ACS) revealed an independent association between reduced risk of recurrent CHD events and triglyceride levels lower than 150 mg/dL.<sup>37</sup> In that study, it was estimated that each 10-mg/dL reduction in triglyceride levels reduced the incidence of death, MI, or recurrent ACS by 1.6% ( $P<0.001$ ) after adjustment for LDL-C reduc-

**Figure 4. Cardiovascular Outcomes Over a Median of 4.9 Years in 1501 Patients With Type 2 Diabetes**



Reprinted with permission from 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(6):1220-1226.<sup>32</sup>

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tion. The long-term effects of triglyceride-lowering therapy in type 2 diabetes remain to be shown. In addition to the recommended therapies listed in **Table 3**, omega-3 fatty acids may also be helpful in lowering triglycerides in patients with type 2 diabetes. A recent systematic review of 24 randomized controlled trials examining triglyceride levels in 1533 patients with type 2 diabetes found that marine-derived, omega-3 polyunsaturated fatty acid supplementation decreased triglycerides by a mean of 7% below baseline values.<sup>38</sup>

### TREATING LOW HDL-C IN DIABETES

It is well established that low HDL-C (<40 mg/dL) is a risk factor for CHD and that raising levels of HDL-C can decrease that risk.<sup>21</sup> Accordingly, the respective capacities of fibrates and niacin to raise HDL-C levels have been evaluated. The HDL-Atherosclerosis Treatment Study (HATS) examined cardiovascular outcomes in patients with metabolic syndrome following combination treatment with niacin plus simvastatin.<sup>39</sup> A subgroup analysis of high-risk patients having coronary artery disease and low HDL-C levels showed that HDL-C levels were significantly increased after 3 years of treatment with niacin plus simvastatin (relative to placebo,  $P<0.0005$ ). Despite an increase in insulin resistance, there was a 60% reduction ( $P=0.03$ ) in death from cardiovascular causes, MI, stroke, or revascularization that accompanied the rise in HDL-C. Further, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study reported that after 12 months of combined treatment with a statin and extended-release niacin in patients with diabetes, there was a rise in HDL-C that correlated significantly with measured reductions in carotid intima-media thickness.<sup>40</sup> In treating diabetic dyslipidemia with niacin, it is important to monitor blood glucose closely since niacin can increase tissue insulin resistance and may exacerbate hyperglycemia when used in patients with diabetes.<sup>8</sup> An additional caution is that combined treatment with statin and niacin raises the risk of myositis or rhabdomyolysis in some patients.<sup>8</sup> The risk of rhabdomyolysis is greater with higher doses of statins and with renal insufficiency. This risk of rhabdomyolysis is also noted with a combination of statin and fibrate therapy, but seems to be lower when statins are combined with fenofibrate than with gemfibrozil.

In the Helsinki Heart Study (HHS), incidence of CHD in men with diabetes was 3.4% after treatment with the fibrate gemfibrozil and 10.5% in the placebo group; however, the difference was not statistically significant.<sup>41</sup> Similarly, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showed that patients with type 2 diabetes who were treated with either fenofibrate or placebo for an average of 5 years had a nonsignificant 11% decrease in coronary events ( $P=0.16$ ).<sup>42</sup> More recently, results of the Diabetes and Combined Lipid Therapy Regimen (DIACOR) study suggest that combination

treatment of patients with type 2 diabetes with simvastatin and fenofibrate may yield cardiovascular benefits beyond treatment with either agent alone.<sup>43</sup> Combination treatment was associated with greater decreases in LDL-C and VLDL as well as greater increases in HDL-C. More importantly for patients with diabetes, there was a shift in the remaining LDL-C to larger, more buoyant particles with combination treatment. Whether these effects will translate to cardiovascular benefits following long-term combination treatment with statins and fibrates in patients with diabetes who are at high risk for cardiovascular events is expected to be shown by the lipid-control arm of the ACCORD study.<sup>44</sup>

### IMPROVING DYSLIPIDEMIA THERAPY IN PATIENTS WITH DIABETES

*Improving adherence to treatment regimens*—Since consistent adherence to statin regimens is proven to be beneficial for patients, improving adherence is a key aspect of diabetes care. One study of patients with type 2 diabetes using statins followed their prescription records over a period of 24 months to determine the medication possession ratio (MPR), which was then used as a gauge of adherence to the statin regimen. A significant correlation ( $P<0.001$ ) was found between the MPR and the measured levels of LDL-C at the end of the study period. The LDL-C treatment goal (ie, <100 mg/dL) was attained by 44% of all the participants, and the MPR was significantly higher among those who reached their goal compared with those who did not (0.82 and 0.61, respectively;  $P<0.05$ ).<sup>45</sup> The importance of monitoring for dyslipidemia as an integral component of comprehensive diabetes therapy was strongly supported in a survey of elderly patients (aged 65 to 75 years) who were receiving primary care for diabetes over a 2-year period.<sup>46</sup> It was found that 31% of the patients surveyed had not had a lipid profile, while an additional 24% received only 1 lipid profile during the 24-month study period. In contrast, the average patient in this study had received approximately 5 HbA<sub>1c</sub> tests within the same time frame, indicating that physicians were testing HbA<sub>1c</sub> levels at near the recommended rate. The latter observation suggests a frequent failure to adequately test lipid profiles in patients who are receiving diabetes care. Most significantly, the same survey reported that patients receiving no lipid profile over the 2-year period were 2.3 times more likely to die from CVD than the patients who received at least 2 lipid profiles during the 24-month study.

A cost/benefit analysis of statin treatment in the Scandinavian Simvastatin Survival Study (4S) and Cholesterol and Recruitment Events (CARE) trials showed that treatment of dyslipidemia in patients with type 2 diabetes is, in fact, cost-effective for reducing cardiovascular mortality over a wide range of baseline LDL-C values.<sup>47</sup> The need for more aggressive statin use was further supported by a study conducted at the Durham Veterans Affairs Health

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Care System, which showed that the closer a patient came to their treatment goal for LDL-C (ie, <100 mg/dL) the less likely it became that their provider would increase the statin dose and ultimately reach the treatment goal.<sup>48</sup> After an educational intervention, health care providers became more likely to titrate the statin doses ( $P=0.023$ ), and 62% of their patients reached their LDL-C target in comparison to 49% of patients treated before the intervention. A particularly noteworthy observation from the same study was that providers were least likely to titrate statin doses in older patients and in patients who had diabetes. In a small study that was aimed at improving patient adherence to colestipol treatment of hypercholesterolemia, a comparison was made between an approach in which physicians and pharmacists implemented a pharmaceutical care program of intensive patient education and motivation as opposed to usual care, which included information about what colestipol is used for and special instructions for taking it.<sup>49</sup> After assessing cardiovascular risk, each patient was assigned an appropriate LDL-C treatment goal according to NCEP ATP-II guidelines. After 52 weeks, significantly more patients in the pharmaceutical care group (29.4%) achieved their LDL-C goals than those in the usual care group (5.0%,  $P<0.05$ ).

**Patient communication**—One method of increasing patient adherence and attaining treatment goals is to improve patient communication. A survey of self-care in patients with diabetes showed that adherence to dietary, exercise, and medication regimens varied widely and

was strongly dependent upon the perceived quality of communication between patients and physicians. For instance, the patients who reported high-quality communication with their physicians were 9 times more likely to adhere to their prescribed dietary modifications than those patients who reported low-quality physician communication. Furthermore, patients who reported high communication scores were 3 times more likely to engage in daily exercise than patients reporting poor communication scores.<sup>50</sup> The ADA recommends that diabetes management, including treatment of dyslipidemia, should be formulated as an alliance between patient, family members, physician, and other members of the health care team.<sup>8</sup> Treatment strategies should provide patient education and guidance in developing problem-solving skills. The treatment goals and other aspects of the care plan should be understood and agreed upon by the patient and the care team.

One effective approach to improve patient communication, called motivational interviewing, hinges on asking open-ended questions and using reflective listening to facilitate a patient's self-examination and determination of their own readiness to change health behaviors as well as to define the motivators or problems that are at work in any detrimental health behavior.<sup>51</sup> When the efficacy of motivational interviewing was tested in women with type 2 diabetes who were participating in a weight control program, the women who received 5 individual motivational interviewing sessions over an 18-month period showed significantly greater weight

### CASE STUDY

Lydia is a 37-year-old Korean American female who recently began diabetes treatment using diet, exercise, and metformin (500 mg bid). Her HbA<sub>1c</sub> is currently 7.2%, and it has been steadily decreasing over the past 4 months. Metformin will be increased to 1000 mg bid. Lydia's BMI is 23 kg/m<sup>2</sup> and she is following her lifestyle modification regimen quite closely.

#### Lydia's lipid profile from today's visit:

**Total cholesterol, 190 mg/dL**  
**LDL-C, 127 mg/dL**  
**HDL-C, 34 mg/dL**  
**Triglycerides, 183 mg/dL**  
**ApoB, 144 mg/dL**



Since Lydia has a family history of CVD (her mother died from an acute MI at 52 years of age), an hs-CRP test was ordered and her level was found to be 4.0 mg/L. Given Lydia's age and the recent onset of her diabetes, she is still in a good position to minimize her cardiovascular risk.

- What cholesterol-lowering regimen would you recommend to Lydia?
- What would you recommend using as a treatment target to help monitor and motivate Lydia's cholesterol-lowering therapy?

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loss after 6 months ( $P=0.01$ ) and 18 months ( $P=0.04$ ). In addition, their HbA<sub>1c</sub> levels were significantly lower after 6 months ( $P=0.02$ ), but not after 18 months.<sup>52</sup> Similarly, in a study of 66 teenagers with type 1 diabetes, inclusion of motivational interviewing produced significantly lower HbA<sub>1c</sub> levels after 12 months ( $P=0.04$ ) and 24 months ( $P=0.003$ ) of diabetes care compared with the control subjects who received nondirective psychological support visits.<sup>53</sup> Subjects receiving motivational interviewing also reported more positive well-being and improved quality of life.

*Conclusion of Lydia's Office Visit: Lydia's family history of CVD and the hs-CRP value of 4.0 mg/dL are concerning; her cardiovascular risk should be reduced as much as possible. Since she is already compliant with previously recommended lifestyle modifications, it is important to acknowledge and encourage her success with those changes. In order to further intensify the lifestyle modification regimen, use the conversation to help her identify in her own mind which lifestyle factors she would be most likely to successfully intensify. Help her to set specific, reachable goals for each lifestyle factor that she feels she is ready to change. Since her BMI is not particularly high or limiting, suggest that she find ways of increasing her daily level of physical activity; this would be especially beneficial for raising her current HDL-C level. A visit with a registered dietitian will also help Lydia identify specific sources of saturated fat, trans fat, and cholesterol in her daily diet and implement dietary changes that will more specifically impact her cholesterol profile. Given Lydia's LDL-C level of 127 mg/dL, initiation of statin therapy is reasonable, especially in view of her other risk factors, namely her family history, type 2 diabetes (a CHD risk equivalent), and her hs-CRP value. Continue to monitor her lipid profile at least once per year, and encourage her to strive for and maintain an LDL-C value of <100 mg/dL.*

### CONCLUSION

The high risk of atherosclerosis and subsequent CHD associated with type 2 diabetes can be reduced substantially with currently available treatments and lifestyle modifications. The ADA recommends screening patients with diabetes for lipid disorders annually, or every 2 years in patients who have a lower risk.<sup>8</sup> In summary, optimal treatment of diabetic dyslipidemia begins with lifestyle modifications that include smoking cessation, increased physical activity, weight loss, and reduction of saturated fats and cholesterol in the diet. Cardiovascular risk can be reduced even late in the course of diabetes. Statin therapy should be instituted in patients with type 2 diabetes and overt CVD, and in patients without CVD who have elevated LDL-C levels and are older than 40 years. Statin therapy should target an LDL-C goal of <70 mg/dL, and modification of triglyceride and HDL-C levels may be considered.

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