Lipid Management in Type 2 Diabetes

Maria P. Solano, MD, and Ronald B. Goldberg, MD

Type 2 diabetes is associated with a marked increased risk of cardiovascular disease (CVD). Individuals with diabetes have an absolute risk of major coronary events similar to that of nondiabetic individuals with established coronary heart disease (CHD). Furthermore, after an acute coronary event, diabetic subjects develop congestive heart failure more frequently and have a higher mortality rate than nondiabetic individuals. A greater burden of risk factors is at least partly responsible for the increased risk of CHD in diabetes. Dyslipidemia is a well-recognized and modifiable risk factor that should be identified early to institute aggressive cardiovascular preventive management.

LIPOPROTEIN PATTERN IN DIABETES

The most typical lipoprotein pattern in diabetes, also known as diabetic dyslipidemia or atherogenic dyslipidemia, consists of moderate elevation in triglyceride levels, low HDL cholesterol values, and small dense LDL particles. This lipoprotein pattern is associated with insulin resistance and is present even before the onset of diabetes. LDL cholesterol levels in type 2 diabetic subjects are generally similar to those found in the general population. Small dense LDL particles are highly atherogenic because of their enhanced susceptibility to oxidative modification and increased uptake by the arterial wall. At triglyceride levels > 132 mg/dl, small LDL particles become common.

Overall, 30–40% of patients with diabetes have triglyceride levels > 200 mg/dl, and 10% have triglycerides > 400 mg/dl. However, in the U.K. Prospective Diabetes Study, despite a high frequency of modestly elevated baseline triglyceride levels (mean baseline 159 mg/dl), a multivariate analysis showed that triglyceride levels did not predict CHD events. LDL cholesterol was the strongest independent predictor of CHD followed by HDL cholesterol, supporting current national guidelines in which LDL lowering is the primary lipid target.

LIPID TARGETS

National Cholesterol Education Panel Guidelines

Diabetes is considered a CHD equivalent. Therefore, lipid targets for individuals with diabetes are the same as those for individuals with established CHD. The primary target is an LDL cholesterol < 100 mg/dl. Recently, the National Cholesterol Education Panel (NCEP) Adult Treatment Panel III (ATP III) lowered the cut point for pharmacological intervention from > 130 to > 100 mg/dl and provided an optional lower target of 70 mg/dl for very-high-risk patients, such as those with diabetes and heart disease.

American Diabetes Association Guidelines

The American Diabetes Association (ADA) has set desirable LDL cholesterol, HDL cholesterol, and triglyceride levels as < 100, > 40 in men/ > 50 in women, and < 150 mg/dl, respectively. The primary treatment strategy, as in the NCEP guidelines, is LDL cholesterol lowering to < 100 mg/dl. The recommended LDL cholesterol level to start pharmacological therapy is > 100 mg/dl in individuals with established CHD and > 130 mg/dl in those without CHD. However, the 2005 recommendations now also state that “statin therapy to achieve an LDL cholesterol reduction of ~ 30% regardless of baseline LDL cholesterol levels may be appropriate.” The second lipid strategy is HDL cholesterol.
1.10–17 The strongest evidence for the beneficial effect of cholesterol lowering with statins in diabetic individuals with and without evidence of CVD and average cholesterol values comes from the Heart Protection Study (HPS)11 and the Collaborative Atorvastatin Diabetes Study (CARDS),10 the first statin trial conducted only in diabetic subjects.

The HPS included 5,963 diabetic individuals, 2,912 of whom had no known CVD. All subjects were > 40 years of age. Treatment with 40 mg of simvastatin reduced the risk of major CHD by 27%. The beneficial effect of simvastatin was similar in diabetic subjects with LDL > and < 116 mg/dl. 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.”

In CARDS, 2,383 individuals (mean age 62 years, mean LDL cholesterol 118 mg/dl) with diabetes but no CVD and at least one risk factor, including hypertension, smoking, retinopathy, and micro- or macroalbuminuria, were randomized to atorvastatin 10 mg per day versus placebo. Treatment with atorvastatin resulted in a 36% reduction in acute

### Table 1. Major Clinical Trials Using Statins

| Study          | Intervention | Baseline LDL Cholesterol (mg/dl) | n     | Diabetes/Total | CVD Outcome                                      | RRR Diabetes (%) | RRR Nondiabetes (%) |
|----------------|--------------|----------------------------------|-------|----------------|--------------------------------------------------|------------------|---------------------|
| **Primary Prevention** |              |                                  |       |                |                                                  |                  |                     |
| CARDS10        | Atorvastatin, 10 mg | 117                            | 2,838 |                | Acute coronary events Stroke                      | 36*              | 48*                 |                     |
| **Primary + Secondary Prevention** |              |                                  |       |                |                                                  |                  |                     |
| HPS11          | Simvastatin, 40 mg | 124                           | 5,963/20,536 | Major CHD event | Any major cardiovascular event                  | 27*              | 24*                 |                     |
| ALLHAT12       | Pravastatin, 10 mg | 129                           | 3,635/10,357 | Major CHD event | 11                                              | 8                |                     |
| ASCOT-LLA13,14 | Atorvastatin, 10 mg | 128                           | 2,532/10,305 | Major CHD event | 16 Total cardiovascular events and procedures    | 23*              | 20*                 |                     |
| **Secondary Prevention** |              |                                  |       |                |                                                  |                  |                     |
| 4S15           | Simvastatin, 10–40 mg | 186                           | 202/4,444 | Total mortality | Major CHD event                          | 43               | 29*                 |                     |
| CARE16         | Pravastatin, 40 mg | 136                           | 586/4,159 | Major CHD event | Expanded end point                             | 13               | 26*                 |                     |
| LIPID17        | Pravastatin, 40 mg | 143                           | 1,077/9,014 | Major CHD event | Any cardiovascular event                      | 19               | 23*                 |

*Statistically significant compared to placebo. Major CHD event: CHD death or non-fatal MI. 4S, Scandinavian Simvastatin Survival Study; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARE, Cholesterol and Recurrent Events trial; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; RRR, relative risk reduction.
CHD events and a 48% reduction in stroke after a median 3.9 years of follow-up, when the study was prematurely ended because of the early positive results. The relative benefit of atorvastatin was similar in individuals whose baseline LDL cholesterol was < 120 mg/dl and those with LDL cholesterol > 120 mg/dl.

**Fibrates**
Support for the use of fibrates in individuals with dyslipidemia comes from the Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial, in which 2,531 men (25% with diabetes) with CHD and low HDL cholesterol and without high LDL cholesterol values (mean LDL cholesterol 108 mg/dl) were randomized to gemfibrozil 1,200 mg daily or placebo. Treatment with gemfibrozil reduced the risk of CHD death, nonfatal myocardial infarction (MI), or confirmed stroke by 24% in both the diabetic and nondiabetic subsets. The change in HDL was the only lipid measure that predicted the CVD benefit.

The Diabetes Atherosclerosis Intervention Study, an angiographic trial conducted only in diabetic individuals, tested the effect of fenofibrate compared with placebo on angiographic end points in 418 individuals with type 2 diabetes and dyslipidemia. The fenofibrate group showed significantly less angiographic progression than the placebo group. Although the study did not have enough power to identify differences in clinical end points, there were fewer cardiovascular events in the fenofibrate compared with the placebo group (18 vs. 23%).

**Niacin**
The only study that has evaluated the effect of niacin monotherapy on cardiovascular events is the Coronary Drug Project, published in 1975. In this study, 1,119 men with history of MI were allocated to treatment with niacin 1–3 g per day, and 2,789 participants received placebo. The mean baseline total cholesterol and triglyceride values were 250 and 177 mg/dl, respectively. The risk of recurrent nonfatal MI was reduced by 27% with niacin. A recent analysis showed that the benefit of niacin treatment on recurrent MI was similar in patients at all levels of blood glucose, including those with fasting blood glucose > 126 mg/dl.

**Combination therapy**
There are no clinical trials evaluating the effect of combination therapy on clinical cardiovascular outcomes. However, evidence for a beneficial effect arising from the addition of niacin therapy to statin treatment was suggested by the HDL Atherosclerosis Treatment Study. In this trial, the effect of combination therapy with simvastatin and niacin compared with placebo on angiographic end points was evaluated in 160 (16% with diabetes) individuals with prior CHD and low HDL cholesterol levels. Simvastatin plus niacin resulted in a significant angiographic benefit. Furthermore, despite the small sample size, treatment with niacin plus simvastatin was associated with a significant 60% reduction in cardiovascular events.

**TREATMENT**

**Lifestyle**
Diet, exercise, and weight loss in overweight individuals are essential in the management of lipid disorders in diabetes. The NCEP and the ADA concur in reducing the intake of saturated and trans-saturated fatty acids to lower LDL cholesterol levels. The NCEP ATP III recommends limiting the intake of saturated fat to < 7% of daily calories and limiting the intake of cholesterol to < 200 mg per day. Additional dietary options to lower LDL cholesterol include increasing the amount of soluble dietary fiber to 10–25 g daily, adding 2 g daily of plant stanols/sterols, and including soy protein in the diet. These interventions have been associated with a 5–15% reduction in LDL cholesterol values. The ATP III also recommends limiting the intake of carbohydrates to < 60% in individuals with elevated triglycerides and low HDL cholesterol levels. The ADA also recommends replacing saturated fat with carbohydrates or monounsaturated fat.

**Diabetes management**
Improving glycemic control in individuals with moderate to severe hyperglycemia regardless of type of treatment is associated with improvement in lipid values. Among the available oral therapeutic options for type 2 diabetes, treatment with metformin and thiazolidinediones has been associated with beneficial effects on lipids. Metformin has been associated with modest reduction in triglyceride levels in hyperlipidemic and hypertensive patients. In a head-to-head comparison study, pioglitazone was associated with significant triglyceride reduction, whereas there was no net triglyceride change with rosiglitazone. Although both agents increased HDL cholesterol and LDL cholesterol, pioglitazone was associated with a greater increase in HDL cholesterol and less LDL cholesterol increase than rosiglitazone.

**P H A R M A C O L O G I C A L L I P I D M A N A G E M E N T**

**LDL cholesterol lowering**
Both the NCEP and the ADA give achievement of the LDL cholesterol target first priority. Both recommend treatment with a statin for all diabetic subjects with an LDL cholesterol > 130 mg/dl. For individuals with LDL cholesterol levels between 100 and 129 mg/dl, both sets of guidelines now support statin therapy to achieve at least a 30–40% LDL cholesterol reduction. Furthermore, the guidelines open the way to initiating statins essentially independent of the LDL cholesterol in patients considered to be at high or very high risk, with the NCEP report setting an optional goal of 70 mg/dl in the latter group of individuals.

Most would argue that individuals with type 2 diabetes and another risk factor are at high risk of cardiovascular
events. In order to achieve a 30–40% LDL cholesterol lowering, at least a moderate dosage of statin (rosuvastatin 5–10 mg per day, atorvastatin 10–20 mg per day, simvastatin 20–40 mg per day, or pravastatin, lovastatin, or fluvastatin 40–80 mg per day) should be used.

Individuals with diabetes who have CVD should be considered for maximal intensity statin or combination therapy. When the NCEP LDL cholesterol target is not achieved with a statin alone, or where statins are not tolerable, combination therapy with etezimibe, bile acid sequestrants, or high-dose niacin should be considered. The major clinical concerns with higher doses of statins are liver toxicity and myopathy. However, the available statins across the range of approved dosages have a good safety and tolerability record, with elevation of liver enzymes > 3 times the upper limit of normal reported in < 1.5% and clinically significant myopathy (creatine phosphokinase ≥ 10 times the upper limit of normal) in < 0.3% of participants in large clinical trials.26–27

Beyond LDL cholesterol lowering

Non-HDL cholesterol. Non-HDL cholesterol is the second therapeutic target according to the ATP III in individuals with triglyceride levels > 200 mg/dl. The therapeutic options for patients with LDL cholesterol < 100 mg/dl (< 70 mg if at very high risk) on statins to lower non-HDL cholesterol to target (< 130 mg/dl) include combination therapy with a fibrate or niacin or alternatively raising the dose of statin or switching to a more potent statin. Fibrates lower triglyceride levels more efficiently than do statins (Table 2) and might be preferred in individuals with significantly elevated triglycerides (e.g., > 300 mg/dl) and at-goal LDL cholesterol values. Fibrate therapy is the first line of treatment for individuals with triglyceride levels > 500 mg/dl in whom triglyceride lowering is given first priority.

HDL cholesterol. The ATP III and the ADA indicate that in high-risk patients with HDL cholesterol levels < 40 mg/dl (< 50 mg/dl in women, according to the ADA), HDL cholesterol raising should be considered, although neither guideline defines a target level. The current limitations in being able to significantly raise HDL cholesterol and the gaps in the understanding of the consequences of HDL-raising interventions on atherogenesis make it premature to construct formal recommendations. This is not to say that fibrates and niacin, the two agents most commonly recommended for HDL raising, do not have value in treatment of dyslipidemia.

| Drug Class | Agents | Lipoprotein Effects | Absolute Contraindications |
|------------|--------|---------------------|---------------------------|
| Statins    |        | LDL cholesterol ↓   | Active or chronic liver disease |
|            |        | 18–55%              |                           |
|            |        | HDL cholesterol ↑   |                           |
|            |        | 5–15%               |                           |
|            |        | Triglycerides ↓ 7–30%|                           |
| Ezetimibe  |        | LDL cholesterol ↓   | In combination with statins, contraindicated in active or chronic liver disease |
|            |        | 15–20%              |                           |
|            |        | HDL cholesterol ↑   |                           |
|            |        | 1–4%                |                           |
|            |        | Triglycerides ↓ 5–10%|                           |
| Bile acid sequestrants | | LDL cholesterol ↓ | Dysbetalipoproteinemia, triglycerides > 400 mg/dl |
|            |        | 15–30%              |                           |
|            |        | HDL cholesterol ↑   |                           |
|            |        | 3–5%                |                           |
|            |        | Triglycerides: no change or increase |                           |
| Nicotinic acid | | LDL cholesterol ↓ | Chronic liver disease, severe gout |
|              |        | 5–25%               |                           |
|              |        | HDL cholesterol ↑   |                           |
|              |        | 15–35%              |                           |
|              |        | Triglycerides ↓ 20–50%|                           |
| Fibric acid derivatives | | LDL cholesterol ↓ | Severe renal disease, severe hepatic disease |
|            |        | 5–20% (may be increased in patients with high triglycerides) |                           |
|            |        | HDL cholesterol ↑   |                           |
|            |        | 10–20%              |                           |
|            |        | Triglycerides ↓ 20–50%|                           |

Adapted from the NCEP ATP III and Physicians’ Desk Reference, 59th ed., 2005.
addition of ezetimibe to a statin will lower LDL cholesterol to goal more often than statin monotherapy will. Bile acid sequestrants may also help to lower LDL cholesterol but should be used with caution because they have a triglyceride-raising effect in hypertriglyceridemic patients.

It is also clear that achievement of all three lipid goals is more likely with statin plus fibrate or statin plus niacin combinations. However, the added complexity and risks of combination therapy in the absence of persuasive clinical trial evidence for additional CVD benefit must place some limitations on the use of these combinations. The presence of CVD should be a clear indication. In those without evident CVD, it would seem appropriate for patients above the age of 40 years or with another major CVD risk factor, such as hypertension. The presence of renal disease is a relative contraindication.

When using combination therapy, patients should be advised to promptly report unexplained muscle complaints. Fenofibrate appears to have significantly fewer pharmacokinetic interactions with statins compared with gemfibrozil, a consideration to take into account when using fibrate-plus-statin combinations. Additionally, in combination therapy, high-dose statins should be avoided to reduce the risk of myopathy. Because of potential worsening of hyperglycemia with niacin, high doses of niacin (>2000 mg) should be used with care, and avoidance of niacin is prudent for individuals with poor glycemic control (i.e., hemoglobin A1c >8%). In addition, adjustment of anti-hyperglycemic therapy may be required.

Finally, ongoing clinical trials in specific diabetic populations evaluating the effect of fibrates alone (the Fenofibrate Intervention and Event Lowering in Diabetes Study) or in combination with statin (the Action to Control Cardiovascular Risk in Diabetes Study) may provide some evidence for more specific recommendations for the management of diabetic dyslipidemia.

REFERENCES

1Haffner SM, Lehto S, Ronnema T, Pyorala L, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229–234, 1998

2Smith JW, Marcus FL, Serokman R: Prognosis of patients with diabetes mellitus after acute myocardial infarction. Am J Cardiol 54:718–721, 1984

3Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, Pyorala K, Tuomilehto J, for the FINMONICA Myocardial Infarction Register Study Group: Impact of diabetes on mortality after the first myocardial infarction. Diabetes Care 21:69–75, 1998

4Demacker PN, Veerkamp MJ, Breddie SJ, Marcovina SM, de Graaf J, Stalenhoef AF: Comparison of the measurements of lipids and lipoproteins versus assay for apolipoprotein B for estimation of coronary artery disease risk: a study in familial combined hyperlipidemia. Atherosclerosis 153:483–490, 2000

5Cowie CC, Harris ML: Physical and metabolic characteristics of persons with diabetes. In Diabetes in America. 2nd ed. Harris MI, Cowie CC, Stern MP, eds. Bethesda, Md: National Institutes of Health, 1995, p. 117–164

6Turner RC, Mills H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR, for the U.K. Prospective Diabetes Study Group: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: UKPDS 23. BMJ 316:823–828, 1998

7Executive Summary of the 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). JAMA 285:2486–2508, 2001

8Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ: The coordinating Committee of the National Cholesterol Education Program; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation, and American Heart Association: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 110:227–239, 2004

9American Diabetes Association: Standards of medical care in diabetes (Position Statement). Diabetes Care 28 (Suppl. 1):S4–S36, 2005

10Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomasson MJ, Mackness MI, Charlton-Menys V, Fuller JH: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDs): multicentre randomised placebo-controlled trial. Lancet 364:685–696, 2004

11Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomized placebo-controlled trial. Lancet 361:2005–2016, 2003

12Diabetes Atherosclerosis Intervention Study Investigators: Fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomized study. JAMA 285:2540–2548, 2001

13The Diabetes Control and Complications Trial Research Group: Effect of intensive treatment of diabetes in type 1 diabetes mellitus on development and progression of certain long-term complications. N Engl J Med 329:977–986, 1993

14The Coronary Drug Project Research Group: Clofibrate and niacin in coronary heart disease. JAMA 231:260–261, 1975

15Canner PL, Furberg CD, McGovern ME: Niacin decreases myocardial infarction and total mortality in patients with impaired fasting glucose or glucose intolerance: results from the Coronary Drug Project [Abstract]. Circulation 106 (Suppl. 2):II-636, 2002

16Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK,
Heart Protection Study Collaborative Group: MCR/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 360:7–22, 2002

Gagne C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, Cho M, Musliner TA, Gumbiner B: Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 90:1084–1091, 2002

Crouse JR III: Hypertriglyceridemia: a contraindication to the use of bile acid binding resins. *Am J Med* 83:243–248, 1987

Athyros VG, Papageorgiou AA, Athyrou VV, Demitradiadis DS, Kontopoulos AG: Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. *Diabetes Care* 25:1198–1202, 2002

Shepherd J: Fibrates and statins in the treatment of hyperlipidemia: an appraisal of their efficacy and safety. *Eur Heart J* 16:5–13, 1995

Guyton JR, Kwiterovich PO, Harper WL, Toth PD, Favrot LK, Kerzner B, Nash SD, Bays HE, Simmons PD. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. *Am J Cardiol* 89:672–678, 2002

Prueksaritanont T, Zhao JJ, Ma B, Roadcap BA, Tang C, Qiu Y, Liu L, Lin JH, Pearson PG, Baillie TA: Mechanistic studies on metabolic interactions between gemfibrozil and statins. *Pharmacol Exp Ther* 301:1042–1051, 2002

Maria P. Solano, MD, is an assistant professor of medicine, and Ronald B. Goldberg, MD, is a professor of medicine in the Division of Diabetes, Endocrinology, and Metabolism, Diabetes Research Institute at the Miller School of Medicine of the University of Miami in Florida.