

Lipid Management in Type 2 Diabetes

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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).¹ Furthermore, after an acute coronary event, diabetic subjects develop congestive heart failure more frequently and have a higher mortality rate than nondiabetic individuals.^{2,3} 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.⁴

Overall, 30–40% of patients with diabetes have triglyceride levels > 200

mg/dl, and 10% have triglycerides > 400 mg/dl.⁵ 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,⁶ 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.⁷ 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.⁸

For individuals with triglyceride levels > 200 mg/dl, the secondary lipid target is the non-HDL cholesterol (total cholesterol minus HDL cholesterol). Non-HDL cholesterol includes all atherogenic lipoproteins that contain apolipoprotein (apo) B, namely, LDL, lipoprotein(a), intermediate-density lipoprotein, and VLDL. The goal for non-HDL cholesterol is 30 mg/dl higher than the LDL target (< 130 mg/dl for diabetic subjects). When triglyceride values are ≥ 500 mg/dl, the first priority is to lower triglyceride levels because of an increased risk of pancreatitis. HDL cholesterol is the third lipid target, and HDL cholesterol-raising strategies may be considered in high-risk individuals with HDL cholesterol levels < 40 mg/dl. However, in the guidelines, HDL cholesterol target levels were not established.

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.”⁹ The second lipid strategy is HDL cholesterol

IN BRIEF

Diabetes is associated with a high risk of cardiovascular disease (CVD). The management of diabetic dyslipidemia, a well-recognized and modifiable risk factor, is a key element in the multifactorial approach to prevent CVD in individuals with type 2 diabetes.

raising, and the third is triglyceride lowering. However, specific treatment targets have not been set.

CLINICAL TRIAL EVIDENCE

Subgroup analyses of intervention trials using statins suggest that the relative cardiovascular benefit of statins is similar among diabetic and nondiabetic participants. There are fewer studies using fibrates or niacin.

Statins

The results of the analyses of the diabetic subgroups in the major statin intervention trials are shown in Table

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						
CARDS ¹⁰	Atorvastatin, 10 mg	117	2,838	Acute coronary events Stroke	36* 48*	— —
Primary + Secondary Prevention						
HPS ¹¹	Simvastatin, 40 mg	124	5,963/20,536	Major CHD event Any major cardiovascular event	27* 22*	27* 24*
ALLHAT ¹²	Pravastatin, 10 mg	129	3,635/10,357	Major CHD event	11	8
ASCOT-LLA ^{13,14}	Atorvastatin, 10 mg	128	2,532/10,305	Major CHD event Total cardiovascular events and procedures	16 23*	44* 20*
Secondary Prevention						
4S ¹⁵	Simvastatin, 10–40 mg	186	202/4,444	Total mortality Major CHD event	43 55*	29* 32*
CARE ¹⁶	Pravastatin, 40 mg	136	586/4,159	Major CHD event Expanded end point	13 25*	26* 23*
LIPID ¹⁷	Pravastatin, 40 mg	143	1,077/9,014	Major CHD event Any cardiovascular event	19 21*	23* 13*

*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,¹⁸ 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,¹⁹ 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,²⁰ 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.²¹

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.²² 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.^{7,23} 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.²⁴ In a head-to-head comparison study,²⁵ 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.

PHARMACOLOGICAL LIPID MANAGEMENT

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 ezetimibe, 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 (creatinine 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

Table 2. Pharmacological Lipid-Modifying Agents

Drug Class	Agents	Lipoprotein Effects	Absolute Contraindications
Statins	Lovastatin	LDL cholesterol ↓	Active or chronic liver disease
	Pravastatin	18–55%	
	Simvastatin	HDL cholesterol ↑	
	Fluvastatin	5–15%	
	Atorvastatin	Triglycerides ↓ 7–30%	
	Rosuvastatin		
Ezetimibe		LDL cholesterol ↓ 15–20% HDL cholesterol ↑ 1–4% Triglycerides ↓ 5–10%	In combination with statins, contraindicated in active or chronic liver disease
Bile acid sequestrants	Cholestyramine	LDL cholesterol ↓	Dysbetalipoproteinemia, triglycerides > 400 mg/dl
	Colestipol	15–30%	
	Colesevalam	HDL cholesterol ↑ 3–5% Triglycerides: no change or increase	
Nicotinic acid		LDL cholesterol ↓ 5–25% HDL cholesterol ↑ 15–35% Triglycerides ↓ 20–50%	Chronic liver disease, severe gout
Fibric acid derivatives	Gemfibrozil	LDL cholesterol ↓	Severe renal disease, severe hepatic disease
	Fenofibrate	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.

< 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.

Combination therapy

The strategy underlying the addition of a second or third agent is to optimize improvements in the lipid profile achieved by initial (usually statin) therapy. This strategy is based on the empirical assumption that further improvement in the lipid profile beyond that initially achieved will yield additional CVD benefit. However, there are as yet no controlled clinical trials comparing statin monotherapy with combination treatment.

It has been clearly shown that the

addition of ezetimibe to a statin will lower LDL cholesterol to goal more often than statin monotherapy will.²⁸ 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.²⁹

It is also clear that achievement of all three lipid goals is more likely with statin plus fibrate or statin plus niacin combinations.^{30–32} 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.³³ 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 (> 2,000 mg) should be used with care, and avoidance of niacin is prudent for individuals with poor glycemic control (i.e., hemoglobin A_{1c} > 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.

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