Lipid Control in the Management of Type 2 Diabetes Mellitus: A Clinical Practice Guideline from the American College of Physicians

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In an effort to provide internists and other primary care physicians with effective management strategies for diabetes care, the Clinical Efficacy Assessment Subcommittee (CEAS) of the American College of Physicians (ACP) decided to develop guidelines on the management of dyslipidemia, particularly hypercholesterolemia, in people with type 2 diabetes mellitus. The CEAS commissioned a systematic review of the currently available evidence on the management of lipids in type 2 diabetes mellitus. The evidence review is presented in a background paper in this issue. On the basis of this systematic review, the CEAS developed recommendations that the ACP Board of Regents then approved as policy.

The target audience for this guideline is all clinicians who care for patients with type 2 diabetes. The target patient population is all persons with type 2 diabetes, including those who already have some form of microvascular complication and, of particular importance, premenopausal women. The recommendations are as follows.

Recommendation 1: Lipid-lowering therapy should be used for secondary prevention of cardiovascular mortality and morbidity for all patients (both men and women) with known coronary artery disease and type 2 diabetes.

Recommendation 2: Statins should be used for primary prevention against macrovascular complications in patients (both men and women) with type 2 diabetes and other cardiovascular risk factors.

Recommendation 3: Once lipid-lowering therapy is initiated, patients with type 2 diabetes mellitus should be taking at least moderate doses of a statin.

Recommendation 4: For those patients with type 2 diabetes who are taking statins, routine monitoring of liver function tests or muscle enzymes is not recommended except in specific circumstances.

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Diabetes mellitus is a leading cause of morbidity and mortality in the United States. Type 2 diabetes mellitus is most common (90% to 95% of persons with diabetes) and affects older adults, particularly those older than 50 years of age. An estimated 16 million Americans have type 2 diabetes, and up to 800 000 new diagnoses are made each year (1, 2). Most adverse diabetes outcomes are a result of vascular complications, which are generally classified as microvascular (such as retinopathy, nephropathy, and neuropathy, although the latter may not be entirely a microvascular disease) or macrovascular (such as coronary artery disease, cerebrovascular disease, and peripheral vascular disease).

To prevent or diminish the progression of microvascular and macrovascular complications, recommended diabetes management necessarily encompasses both metabolic control and control of cardiovascular risk factors (3–5). The need for good glycemic control is supported by the Diabetes Control and Complications Trial (6) in type 1 diabetes and, more recently, the United Kingdom Prospective Diabetes Study in type 2 diabetes (7). In these studies, tight blood sugar control reduced microvascular complications such as nephropathy and retinopathy but had little effect on macrovascular outcomes. Up to 80% of patients with type 2 diabetes will develop or die of macrovascular disease, underscoring the importance of preventing macrovascular complications.

In an effort to provide internists and other primary care physicians with effective management strategies for diabetes care, the American College of Physicians (ACP) decided to develop guidelines on the management of dyslipidemia, particularly hypercholesterolemia, in people with type 2 diabetes. A previous College guideline addressed the critical role of tight blood pressure control in type 2 diabetes mellitus (8, 9). The target audience for this guideline is all clinicians who care for patients with type 2 diabetes. The target patient population is all persons with type 2 diabetes, including those who already have some form of microvascular complication and, of particular importance, premenopausal women. In this guideline we address the following questions.

1. What are the benefits of tight lipid control for both primary and secondary prevention in type 2 diabetes?

2. What is the evidence for treating to certain target levels of low-density lipoprotein (LDL) cholesterol for patients with type 2 diabetes?

3. Are certain lipid-lowering agents more effective or beneficial in patients with type 2 diabetes?

This guideline is based on the systematic review of the evidence presented in the background paper by Vijan and

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colleagues in this issue (10). When Vijan and colleagues analyzed benefit or effectiveness, only studies that measured clinical end points were included. The major clinical end points in trials used to support the evidence for these guidelines were all-cause mortality, cardiovascular mortality, and cardiovascular events (that is, myocardial infarction, stroke, and cardiovascular mortality). No studies of lipid-lowering therapy have been conducted solely in patients with diabetes. Moreover, many trials excluded patients with diabetes. The sample sizes of participants with diabetes were often small, and many studies reported results only for the combined groups. Thus, the reports included in this review are of the subgroup analyses for studies that included patients with diabetes.

The review was stratified into 2 categories. The first category evaluated the effects of lipid management in primary prevention (that is, in patients without known coronary disease). The second category evaluated the effects in secondary prevention (that is, in patients with established coronary disease). A total of 12 lipid-lowering studies presented diabetes-specific data and reported clinical outcomes. A discussion of this evidence follows (for a more detailed description of methodology, refer to the background paper by Vijan and colleagues [10]).

Primary Prevention

Six studies of primary prevention in patients with diabetes were identified. The Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) randomly assigned patients with average cholesterol levels and lower than average high-density lipoprotein (HDL) cholesterol levels to lovastatin, 20 to 40 mg/d, or placebo (in addition to a low-fat and low-cholesterol diet) for an average follow-up of 5.2 years (11). Based on data from the Third National Health and Nutrition Examination Survey, mean total cholesterol level was 5.72 mmol/L (221 mg/dL), mean LDL cholesterol level was 3.88 mmol/L (150 mg/dL), and mean HDL cholesterol level was 0.93 mmol/L (36 mg/dL) for men and 1.03 mmol/L (40 mg/dL) for women. One hundred fifty-five patients had diabetes. Lovastatin therapy led to a relative risk of 0.56 (95% CI, 0.17 to 1.92) for any atherosclerotic cardiovascular event (first fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) and an absolute risk reduction of 0.04 (CI, −0.04 to 0.12), neither of which was statistically significant. The mean LDL cholesterol level at the end of the study was 2.97 mmol/L (115 mg/dL), and the mean HDL cholesterol level was 1.00 mmol/L (39 mg/dL).

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial (ALLHAT-LLT) randomly assigned patients 55 years of age and older who had hypertension and at least one other coronary heart disease (CHD) risk factor to pravastatin, 40 mg/d, or placebo (12). In the subgroup analysis of 3638 patients with type 2 diabetes, the relative risk for CHD events was 0.89 (CI, 0.71 to 1.10); the absolute risk reduction was not reported. This study has been criticized because of the smaller difference between LDL cholesterol levels in the control and intervention groups, which is probably due in part to contamination of the control group by publication of several other lipid-lowering trials during the study.

The Helsinki Heart Study (13) randomly assigned men age 40 to 55 years with elevated non-HDL cholesterol levels to gemfibrozil, 600 mg 2 times per day, or placebo. The mean total cholesterol level was 7.5 mmol/L (290 mg/dL), and mean HDL cholesterol level was 1.23 mmol/L (47.6 mg/dL). In the 135 patients with diabetes, the incidence of CHD at 5 years was 3.4% in the gemfibrozil group and 10.5% in the placebo group. The relative risk was 0.32 (CI, 0.07 to 1.46), and the absolute risk reduction was 0.07 (CI, −0.01 to 0.15). None of these differences were statistically significant (14).

The Heart Protection Study (HPS) included data on both primary and secondary prevention in patients with diabetes who were at high risk for cardiovascular disease (15). The objective of this study was to examine the effects of therapy to lower LDL cholesterol level across a broad range of lipid levels and risk factors. The HPS enrolled patients 40 to 80 years of age with nonfasting total cholesterol levels of at least 3.49 mmol/L (≥135 mg/dL). In the primary prevention group, 3982 patients had diabetes. Treatment with simvastatin, 40 mg, led to reduced risks for CHD events (relative risk, 0.74 [CI, 0.64 to 0.85]; absolute risk reduction, 0.05 [CI, 0.03 to 0.07]).

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) randomly assigned men and women 70 to 82 years of age with a history of cerebral or peripheral vascular disease or risk factors for such disease (such as smoking, hypertension, and diabetes) to pravastatin, 40 mg/d, or placebo (16). In the primary prevention group, 396 patients had diabetes. In these patients, treatment with pravastatin led to a trend toward harm (relative risk, 1.23 [CI, 0.77 to 1.95]; absolute risk reduction, −0.03 [CI, −0.10 to 0.04]). The interaction between diabetes and the treatment group was statistically significant, suggesting that patients with diabetes did substantially worse than those without diabetes.

The Anglo-Scandinavian Cardiac Outcome Trial–Lipid Lowering Arm (ASCOT-LLA) randomly assigned patients age 40 to 79 years without CHD but with hypertension and at least 3 other cardiovascular risk factors (left ventricular hypertrophy, other electrocardiographic abnormalities, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischemic attack, male sex, age ≥ 55 years, microalbuminuria, proteinuria, smoking, ratio of plasma total to HDL cholesterol of 6 or higher, or family history of premature CHD) to atorvastatin, 10 mg/d, or placebo (17). The diabetes subgroup, 2532 patients who had hypertension and at least 2 other risk factors, had low

event rates of 3.6% in the control group and 3.0% in the intervention group. Thus, lipid-lowering treatment, with a relative risk of 0.84 (CI, 0.55 to 1.29) and an absolute risk reduction of 0.006 (CI, −0.008 to 0.019), did not lead to statistically significant improvements in the diabetes group.

Secondary Prevention

Eight trials reported on secondary prevention in patients with diabetes. The first, the Scandinavian Simvastatin Survival Study (4S), randomly assigned patients with coronary disease to simvastatin, 20 mg, or placebo (18). In a secondary analysis of the 202 patients with diabetes, simvastatin led to large benefits (relative risk for cardiovascular events, 0.50 [CI, 0.33 to 0.76]; absolute risk reduction, 0.23 [CI, 0.10 to 0.35]). Of note is the relatively high event rate in the control group (45%) compared with those seen in other trials.

The Cholesterol and Recurrent Events (CARE) trial randomly assigned patients with previous myocardial infarction to pravastatin, 40 mg/d, or placebo (19). Pravastatin improved CHD outcomes in the 586 patients with diabetes (relative risk for cardiovascular events, 0.78 [CI, 0.62 to 0.99]; absolute risk reduction, 0.08 [CI, 0.01 to 0.16]). Results were reported as stratified by baseline LDL cholesterol levels and showed that for the overall study sample, those with baseline levels below 3.23 mmol/L (<125 mg/dL) did not benefit from lipid-lowering therapy while those with LDL cholesterol levels of at least 3.23 mmol/L (≥125 mg/dL) benefited substantially. The small sample size precluded a similar stratified analysis in the patients with diabetes.

The HPS examined the impact of lipid-lowering therapy in secondary prevention in 20 536 patients with coronary disease, other occlusive arterial disease, or diabetes (15). Treatment was with simvastatin, 40 mg/d, or placebo. There was no dose adjustment by baseline lipid levels. Among patients with diabetes, the relative risk for any cardiovascular event was 0.89 (CI, 0.79 to 1.00) in the simvastatin group, and the absolute risk reduction was 0.04 (CI, 0.00 to 0.09).

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial randomly assigned patients with known heart disease to pravastatin, 40 mg/d, or placebo (20). In the subgroup of 782 patients with diabetes, the relative risk for a cardiovascular event was 0.84 (CI, 0.64 to 1.11) and the absolute risk reduction was 0.04 (CI, −0.02 to 0.09). Neither of these was statistically significant.

The Lescol Intervention Prevention Study (LIPS) was a trial conducted in patients who had undergone percutaneous coronary intervention (21). Researchers randomly assigned patients to fluvastatin, 80 mg/d, or placebo. In the 202 patients with type 2 diabetes, fluvastatin was effective in preventing CHD events (relative risk, 0.53 [CI, 0.29 to 0.97]; absolute risk reduction, 0.16 [CI, 0.03 to 0.29]).

The Post–Coronary Artery Bypass Graft (Post-CABG) trial randomly assigned patients who had undergone coronary artery bypass grafting to "aggressive" LDL cholesterol targets of 1.55 to 2.20 mmol/L (60 to 85 mg/dL) or "moderate" targets of 3.36 to 3.62 mmol/L (130 to 140 mg/dL) (22). Lovastatin was used as the primary agent, and cholestyramine was added if goals were not achieved. Most patients did not reach the intensive goal; the mean achieved LDL cholesterol level ranged from 2.40 to 2.51 mmol/L (93 to 97 mg/dL) over the course of the study. One hundred sixteen patients in the trial had diabetes. Aggressive LDL cholesterol lowering led to a relative risk of 0.53 (CI, 0.18 to 1.60) and an absolute risk reduction of 0.12 (CI, −0.03 to 0.27). Neither of these was statistically significant.

The Veterans Administration High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) was a secondary prevention study whose intervention and goal were different from the others (23). This study targeted patients with the low-HDL, low-LDL syndrome (HDL cholesterol level ≤ 1.03 mmol/L 40 mg/dL]; LDL cholesterol level ≤ 3.62 mmol/L [≤140 mg/dL]), which is very common in patients with diabetes or insulin resistance. The study enrolled men younger than 74 years of age who had documented coronary disease. Treatment was with gemfibrozil, 1200 mg/d, or placebo. In the diabetes subgroup (n = 627), the relative risk for cardiovascular events was 0.76 (CI, 0.57 to 1.01) and the absolute risk reduction was 0.08 (CI, 0.01 to 0.15). In a follow-up article, inclusion of patients with undiagnosed diabetes in this subgroup reduced the risks further (relative risk, 0.68; absolute risk reduction, 10%) (24). Of interest, these analyses also suggest that much of the benefit in this study was in patients with diabetes and that fasting plasma insulin levels were a major indicator of the success of therapy.

Meta-Analysis

Vijan and colleagues conducted a meta-analysis of the trial results for the diabetes subgroups (10). For the primary prevention studies, the pooled relative risk for cardiovascular events with lipid-lowering therapy was 0.78 (CI, 0.67 to 0.89) and the pooled absolute risk reduction was 0.03 (CI, 0.01 to 0.04); the pooled estimate of the number needed to treat to prevent an event was 34.5 for a weighted trial average of 4.3 years. Of note, the results of ALLHAT-LLT are included in the pooled estimates of relative risk but not those of absolute risk reduction because the latter data were not available.

For the secondary prevention studies, the pooled relative risk for cardiovascular events with lipid-lowering therapy was very similar to that for primary prevention: 0.76 (CI, 0.59 to 0.93). However, because of the greater absolute risk among patients with known coronary artery disease, the pooled absolute risk reduction was more than twice as high (0.07 [CI, 0.03 to 0.12]) and the number needed to treat for benefit was only 13.8 for a weighted

trial average of 4.9 years. In trials of both primary and secondary prevention, Vijan and colleagues conducted sensitivity analyses excluding the trials that used gemfibrozil (the Helsinki Heart Study for primary prevention and VA-HIT for secondary prevention), but this did not change the estimates of relative risk or absolute risk reduction (10).

Safety of Lipid-Lowering Agents

The current literature suggests that statins are extremely safe. Although rates of discontinuation and nonadherence in clinical trials are approximately 15% or more in many cases, rates of discontinuation typically are not different from those of placebo. Rates of elevated levels of liver or muscle enzymes did not differ between the statin and placebo groups in recent large-scale studies. For example, in the HPS, rates of elevated alanine aminotransferase levels above twice the upper limit of normal were 1.8% in the simvastatin group and 1.6% in the placebo group, and rates of elevated creatine kinase levels were 0.3% in the simvastatin group and 0.2% in the placebo group (15). Neither of these differences was statistically significant. Similarly, among the 5804 patients in PROSPER, only 1 person in each group had an alanine aminotransferase or aspartate aminotransferase level more than 3 times the upper limit of normal (16). In addition, no patients had rhabdomyolysis and 36 patients in the pravastatin group had myalgia compared with 32 in the placebo group. Based on the safety of these drugs, routine monitoring of liver or muscle enzymes is probably not warranted except in patients with symptoms, patients who have liver enzyme abnormalities at baseline, or patients taking drugs that interact with statins to increase the risk for adverse events.

Summary

Given the markedly elevated risk for cardiovascular events in most persons with type 2 diabetes, preventing cardiovascular disease through aggressive management of cardiovascular risk factors is of utmost importance. Optimizing treatment of hypertension, smoking cessation, and lipid control provides substantial benefit, at least to the average patient with type 2 diabetes. The evidence suggests that lipid-lowering medication leads to a 22% to 24% reduction in major cardiovascular events in patients with diabetes. On the basis of the current literature, statins are the agents of choice. The meta-analysis by Vijan and colleagues (10) suggests that there is good evidence for the empirical use of at least moderate doses of statins in patients at average or above-average risk for cardiovascular disease.

However, the evidence on targeting specific levels of LDL cholesterol is not clear. Most of the trials did not set specific target levels or used different levels than are currently recommended. In addition, a reasonable argument can be made in favor of using gemfibrozil as first-line therapy (compared with statins) for patients with low HDL and LDL cholesterol levels. Although the relative risk reductions were very similar for both primary and secondary prevention, the average absolute risk reduction was more than twice as high for persons with known coronary artery disease (secondary prevention) than for those without (primary prevention).

Moreover, even among the secondary prevention trials, the absolute risk reduction was the largest in the 3 trials with the highest-risk participants: 4S, which had participants with by far the highest baseline LDL cholesterol levels, and LIPS and Post-CABG, which were conducted in the highest-risk patients (those who had procedures for coronary revascularization). In contrast, only one of the primary prevention studies showed statistically significant benefit in patients with diabetes, and the observed benefits were quite small or absent in studies in which patients with diabetes had low baseline risk (16, 17). As a result, clinicians should use caution in extrapolating the average results from the primary prevention meta-analysis to patients at lower than average risk (such as younger patients with diabetes who have no other major cardiovascular risk factors).

Future studies should evaluate the relative effectiveness of specific strategies, such as different targets for LDL cholesterol level versus different doses of empirical statin therapy and combination therapy, and should also consider the potential effects of statins beyond lipid-lowering.

Recommendations

Recommendation 1: Lipid-lowering therapy should be used for secondary prevention of cardiovascular mortality and morbidity for all patients (both men and women) with known coronary artery disease and type 2 diabetes.

Although the relative risk reductions were very similar for both primary and secondary prevention, the average absolute risk reduction was more than twice as high for those with known coronary artery disease (secondary prevention) than for those without (primary prevention). This is a reflection of the fact that the secondary prevention studies universally had higher risks for cardiovascular outcomes, on average; indeed, the 4.3-year risk in the control group ranged from 3.6% to 18.6% in the primary prevention studies, but the 4.9-year risk ranged from 22.8% to 45.4% in the secondary prevention studies.

Statins have the most cumulative evidence of benefit and should be the agent of choice for secondary prevention. The one exception, based on the VA-HIT, is for patients with diabetes and low levels of both HDL and LDL cholesterol. In the VA-HIT, treatment with gemfibrozil, 1200 mg/d, led to an absolute risk reduction of 10%. Thus, these patients may benefit more from gemfibrozil than from a statin, but to date there are no head-to-head comparisons of the drugs alone or in combination.

Table. **Treatments Used in the Trials Reviewed**

Primary prevention trials
Atorvastatin, 10–20 mg/d
Lovastatin, 20–40 mg/d
Pravastatin, 40 mg/d
Simvastatin, 40 mg/d
Secondary prevention trials
Fluvastatin, 80 mg/d
Lovastatin, 40–80 mg/d
Pravastatin, 40 mg/d
Simvastatin, 20 mg/d and 40 mg/d
Gemfibrozil, 1200 mg/d*

* For secondary prevention in patients with low levels of both low-density and high-density lipoprotein cholesterol.

Recommendation 2: Statins should be used for primary prevention against macrovascular complications in patients (both men and women) with type 2 diabetes and other cardiovascular risk factors.

The primary prevention studies that showed the most benefit with treatment were the ones that included patients with other significant cardiovascular risk factors, specifically age older than 55 years, hypertension, smoking, left ventricular hypertrophy, previous cerebrovascular disease, and peripheral arterial disease. The difference in the cardiovascular risk profiles of the 2 sexes in the general population is not as apparent in the diabetes population. No strong evidence supports exact thresholds for initiating treatment or treating to specific target LDL or total cholesterol levels in patients with type 2 diabetes. Therefore, the decision to initiate treatment on the basis of thresholds or to treat to a target should be made after shared discussion between the patient and the clinician. No clinical trial evidence informs the use of statins in low-risk persons younger than 55 years of age who have type 2 diabetes and no other cardiovascular risk factors.

Recommendation 3: Once lipid-lowering therapy is initiated, patients with type 2 diabetes mellitus should be taking at least moderate doses of a statin.

The current literature provides strong support for the use of moderate doses of statins in patients with diabetes (**Table**). Inference from observational studies suggests the benefit of targeted treatment (25). However, the trials that reported experience in patients with diabetes did not set specific target levels for LDL cholesterol or used different target levels than those currently recommended.

Although the achieved LDL cholesterol levels in the trials have consistently been below 3.1 mmol/L (<120 mg/dL), different studies have found differing benefit for lower target levels. The CARE study found no benefit for lipid-lowering therapy in patients with initial LDL cholesterol levels below 125 mg/dL. However, the LIPID trial did not identify any such threshold. The HPS, which had the largest diabetes subgroup, demonstrated a consistent (close to 25%) relative risk reduction and a 5% to 7% absolute risk reduction in cardiovascular events with statin therapy regardless of initial LDL cholesterol levels, even among patients whose initial levels were below the National Cholesterol Education Program target of 100 mg/dL. This lack of clarity may relate to the mechanism of action of statins, since their benefit may be derived from their LDL cholesterol–lowering effects or from other effects such as plaque stabilization, improved endothelial function, or effects on C-reactive protein (26).

The primary prevention trials do not provide adequate evidence to guide drug choice because most of the diabetes subgroups were too small. On the basis of the current clinical trial evidence, it would be reasonable to use the following: atorvastatin, 20 mg/d; lovastatin, 40 mg/d; pravastatin, 40 mg/d; or simvastatin, 40 mg/d.

The following agents and doses were used in clinical trials for secondary prevention: fluvastatin, 80 mg/d; lovastatin, 40 to 80 mg/d; pravastatin, 40 mg/d (2 trials); and simvastatin, 20 mg/d and 40 mg/d.

In patients with low levels of both LDL and HDL cholesterol, gemfibrozil, 1200 mg/d, has also shown benefit.

No clinical trials inform the use of one statin over another. Given the unclear evidence on the benefit of treating to target LDL cholesterol levels, more aggressive titration of statins or use of combination lipid-lowering treatment titrated on the basis of LDL cholesterol levels should be a shared decision between the physician and the patient.

Recommendation 4: For those patients with type 2 diabetes who are taking statins, routine monitoring of liver function tests or muscle enzymes is not recommended except in specific circumstances.

The current literature suggests that statins are extremely safe. Although discontinuation and nonadherence rates are approximately 15% or more in many clinical trials, rates of discontinuation typically do not differ from those of placebo. Rates of elevated liver or muscle enzyme levels did not differ between the statin and placebo groups in recent large-scale studies. On the basis of the safety data pertaining to these drugs, routine monitoring of muscle enzymes and liver function tests is probably not warranted unless patients have symptoms (27, 28), have baseline abnormalities of liver function tests or myopathy, or are taking other drugs that interact with statins to increase the risk for adverse events.

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