

Pharmacologic Lipid-Lowering Therapy in Type 2 Diabetes Mellitus: Background Paper for the American College of Physicians

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Background: Cardiovascular disease is the primary complication and cause of death in patients with type 2 diabetes mellitus. Modification of cardiovascular risk factors may improve patient outcomes.

Purpose: To evaluate the effectiveness of pharmacologic lipid-lowering therapy on outcomes in type 2 diabetes mellitus.

Data Sources: Review of the literature.

Study Selection: Randomized trials evaluating clinical outcomes of lipid-lowering treatment in patients with diabetes.

Data Extraction: Studies were identified by searching the Cochrane Library, MEDLINE, meta-analyses, review articles, and inquiries to experts. The Cochrane Library and MEDLINE searches were done in September 2002. Data were abstracted onto standardized forms by a single reviewer and were confirmed by a second reviewer.

Data Synthesis: Meta-analysis of 6 primary prevention studies showed that lipid-lowering medications reduced risks for cardiovascular outcomes (relative risk, 0.78 [95% CI, 0.67 to 0.89]; absolute risk reduction, 0.03 [CI, 0.01 to 0.04] in 4.3 years of treatment); 1 major cardiovascular event was prevented by treat-

ing 34 to 35 patients. Meta-analysis of 8 studies of secondary prevention showed a similar relative risk (0.76 [CI, 0.59 to 0.93]) but more than twice the absolute risk reduction (0.07 [CI, 0.03 to 0.12] in 4.9 years of treatment) and a number needed to treat for benefit of 13 to 14. Most studies compared a lipid-lowering drug with placebo but did not evaluate the effect of reaching specific cholesterol levels. The benefit of lipid lowering with a fixed dose of a statin appeared to be similar regardless of starting cholesterol levels.

Limitations: Target cholesterol levels and the effectiveness of dose titration (or the use of multiple agents) have not been rigorously examined.

Conclusions: In patients with type 2 diabetes, treatment with lipid-lowering agents reduces cardiovascular risk. Most patients, including those whose baseline low-density lipoprotein cholesterol levels are below 2.97 mmol/L (<115 mg/dL), and possibly below 2.59 mmol/L (<100 mg/dL), benefit from statins. Moderate doses of these drugs suffice in most patients with diabetes.

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Type 2 diabetes mellitus is a common disease that is increasing to near epidemic levels in industrialized nations (1, 2). Diabetes is associated with substantial risk for morbidity and premature mortality (3, 4). Most adverse diabetes outcomes are due to vascular complications, either at a macrovascular level (that is, coronary artery disease, cerebrovascular disease, or peripheral vascular disease) or a microvascular level (that is, retinopathy, nephropathy, or neuropathy) (5). Macrovascular complications are more common and severe; up to 80% of patients with type 2 diabetes will develop or die of macrovascular disease, and the costs associated with macrovascular disease are an order of magnitude greater than those for microvascular disease (6).

Given the epidemiology of diabetes complications, management of cardiovascular risk has been emphasized in people with diabetes. Modifying cardiovascular risk by treating hypertension or by using lipid-lowering agents is of tremendous importance and may be more effective and cost-effective than treating hyperglycemia (7, 8). This paper focuses on the evidence behind the use of lipid-lowering agents in type 2 diabetes. Patients with diabetes typically have low high-density lipoprotein (HDL) cholesterol levels, high triglyceride levels, and average low-density lipoprotein (LDL) cholesterol levels; LDL cholesterol particles in people with diabetes tend to be smaller, denser, and possibly more atherogenic (9, 10). The elevated cardiovas-

cular risk in patients with type 2 diabetes makes these patients strong candidates for treatment with lipid-lowering medications.

METHODS

The literature review was limited to randomized, controlled trials of drug therapy that included patients with diabetes. Only studies that measured major clinical end points were included. Major clinical end points were defined as major cardiovascular events (for example, cardiovascular mortality, myocardial infarction, stroke), cardiovascular mortality, and total mortality. Of note, many of the trials reported somewhat different clinical end points in the patients with diabetes. All included cardiovascular mortality and myocardial infarction in their composite end point; some included stroke and revascularization, and one included unstable angina. We used the primary reported data directly from the published study in our review. We also subdivided the literature review into 2 categories. The first category evaluated the effects of lipid management in primary prevention (that is, patients without known cardiovascular disease); the second evaluated the effects in secondary prevention.

We used several sources to identify the relevant literature. We started with a search of the Cochrane Library. We then performed a MEDLINE search in September 2002.

We used the keywords *exp diabetes mellitus* and *exp lipids [therapy or prevention and control]* and limited the search to randomized, controlled trials and human studies. The final search produced 919 results. Of these, most were discarded because they did not measure major clinical end points, did not report outcomes for patients with diabetes, were observational in nature, or were reviews or editorials. We then updated the search through consultation with experts and through references from the identified articles, meta-analyses, and review articles.

The primary author extracted data from the primary study reports. Accuracy and quality of the abstraction were confirmed through reabstraction and comparison with the original abstraction. The outcomes were broken into categories as described earlier, and data on absolute and relative risk reduction and numbers needed to treat for benefit were derived from the primary reports or were calculated in standard fashion (11).

The results of the studies were then combined by using meta-analytic techniques. We pooled data for both relative and absolute risks. A Mantel-Haenszel test was done to test for heterogeneity. In the analyses of secondary prevention, the data had substantial heterogeneity, so the pooled risk ratios and differences were calculated by using the DerSimonian and Laird method with a random-effects model. Sensitivity analyses were done by excluding studies that appeared to be outliers to ascertain the source of the heterogeneity. All analyses were done by using the statistical package Stata (Stata Corp., College Station, Texas).

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DATA SYNTHESIS

No studies of lipid-lowering therapy that reported cardiovascular outcomes were conducted solely in patients with diabetes, but several studies reported diabetes subgroup analyses. Sample sizes of participants with diabetes were often small, so most of the studies presented data only on combined cardiovascular events (for example, cardiovascular mortality, nonfatal myocardial infarction, stroke, and coronary revascularization). In several cases, diabetes was an exclusion criterion or very few patients with diabetes were included; for example, in the West of Scotland Coronary Prevention Study, about 1% of patients (76 of 6595) had diabetes, and results were not presented for this subgroup (12). We found a total of 12 lipid-lowering studies that presented diabetes-specific data and reported clinical outcomes. Of these studies, 4 were focused on primary prevention, 6 were focused on secondary prevention, and 2 presented data on both. The general study characteristics, including the effect of interventions of lipid levels, are presented in Table 1.

Primary Prevention Trials

We identified 6 studies that evaluated primary prevention for patients with diabetes. The Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) randomly assigned patients with average cholesterol levels to receive lovastatin, 20 mg/d, or placebo (13). The daily dose of lovastatin was increased to 40 mg if the LDL cholesterol level was above 2.84 mmol/L (>110 mg/dL). One hundred fifty-five patients had diagnosed diabetes at study entry. Lovastatin therapy led to a relative risk of 0.56 (95% CI, 0.17 to 1.92) for any coronary heart disease (CHD) event and an absolute risk reduction of 0.04 (CI, -0.04 to 0.12), neither of which was statistically significant.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid-Lowering Trial (ALLHAT-LLT) randomly assigned patients who were 55 years of age or older and who had hypertension and at least one other CHD risk factor to pravastatin, 40 mg/d, or placebo (14). Only 14% of patients had known CHD at baseline; thus, this was essentially a trial of primary prevention. In the subgroup 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. Some have criticized this trial because the difference in LDL cholesterol levels between the intervention and control groups was smaller than in other studies (17%, or 0.62 mmol/L [24 mg/dL] at 4 years). This was due in part to contamination of the control arm caused by publication of several other lipid-lowering studies during the trial.

The Helsinki Heart Study was a randomized, controlled primary prevention trial of gemfibrozil in patients with elevated non-HDL cholesterol levels (primarily triglyceride and LDL cholesterol levels) (15). One hundred thirty-five patients in the study had diabetes. The incidence of CHD was 3.4% in the gemfibrozil group and 10.5% in the placebo group (relative risk, 0.32 [CI, 0.07 to 1.46]; absolute risk reduction, 0.07 [CI, -0.01 to 0.15]) (16). Given the small sample size, these differences were not statistically significant.

The Heart Protection Study (HPS) included data on both primary and secondary prevention in patients with diabetes (17). The goal of this large study was to examine the effects of LDL cholesterol-lowering therapy across a broad range of lipid levels and risk factors. In the primary prevention group, 3982 patients had diabetes. Treatment with simvastatin 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 elderly patients (age 70 to 82 years) to pravastatin, 40 mg/d, or placebo (18). This study also evaluated both primary and secondary prevention. In total, 623 patients had diabetes; of these, 396 were in the primary prevention group. In this group, pravastatin led to trend toward harm, with a relative risk of

Table 1. Studies of Lipid-Lowering Therapy in Type 2 Diabetes Mellitus: Intervention, Lipid Goals, and Achieved Lipid Levels*

Study (Reference)	Type of Prevention	Intervention	LDL Cholesterol Target, Intervention Group	LDL Cholesterol Level, Intervention Group	LDL Cholesterol Level, Placebo Group
			mmol/L (mg/dL)		
AFCAPS/TexCAPS (13)	Primary	Lovastatin, 20 mg/d, titrated to 40 mg/d if LDL cholesterol level >2.84 mmol/L (>110 mg/dL)	<2.84 (<110)	2.97 (115)	4.03 (156)
ALLHAT-LLT (14)	Primary	Pravastatin, 40 mg/d	None	2.72 (105)	3.34 (129)
HHS (15, 16)†	Primary	Gemfibrozil, 600 mg twice daily	None	4.73 (183)	4.91 (190)
HPS (17)	Primary	Simvastatin, 40 mg/d	None	2.30 (89)	3.31 (128)
PROSPER (18)	Primary	Pravastatin, 40 mg/d	None	2.77 (107)	3.78 (146)
ASCOT-LLA (19)	Primary	Atorvastatin, 10 mg/d	None	2.33 (90)	3.26 (126)
4S (20)	Secondary	Simvastatin, 20 mg/d, titrated to 40 mg/d if total cholesterol level > 5.17 mmol/L (>200 mg/dL)	Total cholesterol target, 5.17 (200)	3.03 (117)	4.81 (186)
CARE (21)	Secondary	Pravastatin, 40 mg/d; cholestyramine added if LDL cholesterol level ≥4.53 mmol/L (≥175 mg/dL)	Not specified	2.53 (98)	3.59 (139)
HPS (17)	Secondary	Simvastatin, 40 mg/d	None	2.30 (89)	3.31 (128)
LIPID (22)	Secondary	Pravastatin, 40 mg/d	None	2.92 (113)	3.88 (150)
LIPS (23)	Secondary	Fluvastatin, 40 mg twice per day	None	2.46 (95)	3.80 (147)
Post-CABG (24)	Secondary	LDL cholesterol goal of 1.55–2.20 mmol/L (60–85 mg/dL) vs. 3.36–3.62 mmol/L (130–140 mg/dL) using lovastatin	1.55–2.20 (60–85)	2.40 (93)	3.52 (136)
PROSPER (18)	Secondary	Pravastatin, 40 mg/d	None	2.77 (107)	3.78 (146)
VA-HIT (25, 26)	Secondary	Gemfibrozil, 600 mg twice daily	‡	‡	‡

* 4S = Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS = Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm; CARE = Cholesterol and Recurrent Events trial; HHS = Helsinki Heart Study; HPS = Heart Protection Study; LDL = low-density lipoprotein; LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease trial; LIPS = Lescol Intervention Prevention Study; Post-CABG = Post-Coronary Artery Bypass Graft trial; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; VA-HIT = Veterans Administration High-Density Lipoprotein Cholesterol Intervention Trial.

† In the HHS, gemfibrozil reduced triglyceride levels by 36% (0.72 mmol/L [64 mg/dL]) and increased high-density lipoprotein cholesterol levels by 10% (0.1 mmol/L [4 mg/dL]).

‡ VA-HIT targeted patients with low high-density lipoprotein cholesterol levels as its primary intervention. The increase in high-density lipoprotein cholesterol levels was 0.05 mmol/L (2 mg/dL) in patients with diabetes, and the decrease in triglyceride levels was 0.37 mmol/L (33 mg/dL). Treatment did not affect levels of LDL cholesterol.

1.23 (CI, 0.77 to 1.95) and an absolute risk reduction of –0.03 (CI, –0.10 to 0.04) (Shepherd J, Blauw GJ, Murphy MG. Personal communication). This contrasted with the primary results of the trial, which showed a positive effect of pravastatin. Indeed, the interaction between the diabetes and treatment groups was statistically significant, suggesting that patients with diabetes did substantially worse than those without diabetes.

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA) randomly assigned patients without CHD but with hypertension and at least 3 other cardiovascular risk factors to atorvastatin, 10 mg/d, or placebo (19). A total of 2532 patients with diabetes who also had hypertension and 2 or more other risk factors participated in the study. The patients with diabetes had surprisingly low event rates of 3.6% in the control group and 3.0% in the intervention group. 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 outcomes in the diabetes subgroup.

Secondary Prevention Trials

Eight trials reported data on secondary prevention of coronary disease in patients with diabetes. The Scandinavian Simvastatin Survival Study (4S) randomly assigned patients with heart disease to simvastatin or placebo (20). In a secondary analysis of 202 patients with diabetes at baseline, simvastatin led to large benefits, with a relative risk for cardiovascular events of 0.50 (CI, 0.33 to 0.76) and an absolute risk reduction of 0.23 (CI, 0.10 to 0.35). Of note, the event rate in this trial was very high (45% in the control group) relative to other studies.

The Cholesterol and Recurrent Events (CARE) trial randomly assigned patients with myocardial infarction to pravastatin, 40 mg/d, or placebo (21). In the subgroup of 586 patients with diabetes, pravastatin improved CHD outcomes, with a relative risk for cardiovascular events of 0.78 (CI, 0.62 to 0.99) and an absolute risk reduction of 0.08 (CI, 0.01 to 0.16). In the overall study sample, the authors risk-stratified patients by baseline LDL cholesterol levels and found that those with baseline levels less than 3.23 mmol/L (<125 mg/dL) did not benefit from lipid-

lowering therapy, while those with baseline levels of 3.23 mmol/L (125 mg/dL) or greater received substantial benefit. However, small sample size precluded a stratified analysis in patients with diabetes.

The HPS also reported the impact of lipid-lowering therapy in secondary prevention in patients with diabetes (17). The intervention was again a standard dosage of simvastatin, 40 mg/d, without dose adjustment by lipid levels. In patients with diabetes, the relative risk for any cardiovascular event in the intervention group was 0.89 (CI, 0.79 to 1.00) and the absolute risk reduction was 0.04 (CI, 0.00 to 0.09).

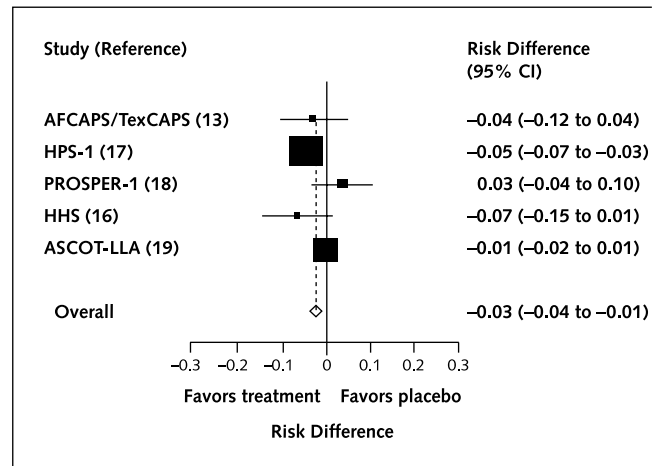
The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial randomly assigned patients with known heart disease to pravastatin, 40 mg/d, or placebo (22). In the subgroup of 782 patients with diabetes, the relative risk for a cardiovascular event was 0.84 (CI, 0.64 to 1.11) and the absolute 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 (23). Patients were randomly assigned to fluvastatin, 80 mg/d, or placebo. In the 202 patients with type 2 diabetes, fluvastatin was effective in preventing CHD events, with a relative risk of 0.53 (CI, 0.29 to 0.97) and an absolute risk reduction of 0.16 (CI, 0.03 to 0.29).

The Post-Coronary Artery Bypass Graft (Post-CABG) trial randomly assigned patients who had undergone coronary bypass grafting to an LDL cholesterol level target of 1.55 to 2.20 mmol/L (60 to 85 mg/dL) or 3.36 to 3.62 mmol/L (130 to 140 mg/dL) (24). Lovastatin was used as the primary agent, and cholestyramine was added if goals were not achieved. Of note, 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 that had a different intervention and goal than the others, which all used statins with a goal of reducing LDL cholesterol levels (25). The VA-HIT targeted patients with the low-HDL, low-LDL syndrome (HDL cholesterol level \leq 1.03 mmol/L [\leq 40 mg/dL]; LDL cholesterol level \leq 3.62 mmol/L [\leq 140 mg/dL]), which is very common in patients with diabetes or insulin resistance. 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 those with undiagnosed diabetes in this subgroup improved the risks further (relative risk, 0.68; absolute risk reduction, 10%). Of

Figure 1. Meta-analysis of the absolute risk reduction of lipid-lowering as primary prevention in patients with diabetes.



Note that the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is not included in this figure because data on absolute risk reduction in the diabetes subgroup were not available. AFCAPS/TexCAPS = Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm; HHS = Helsinki Heart Study; HPS-1 = Heart Protection Study (primary prevention arm); PROSPER-1 = Prospective Study of Pravastatin in the Elderly at Risk (primary prevention arm).

interest, these analyses also suggested 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 (26).

In PROSPER, elderly patients (age > 70 years) were randomly assigned to pravastatin, 40 mg/d, or placebo (18). This study also included a secondary prevention arm, which involved 227 patients with diabetes. Pravastatin led to a trend toward harm, with a relative risk of 1.26 (CI, 0.85 to 1.87) and an absolute risk reduction of -0.07 (CI, -0.19 to 0.05) (Shepherd J, Blauw GJ, Murphy MB. Personal communication).

Meta-Analysis

We conducted meta-analyses of the trial results. For primary prevention, we did not find substantial heterogeneity between studies ($P = 0.18$); thus, we used fixed-effects analyses. 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 number needed to treat to prevent an event was 34.5 for a weighted trial average of 4.3 years (Table 2, Figure 1). Of note, the results of ALLHAT are included in the pooled estimates of relative risk but not those of absolute risk reduction because these data were not available. Exclusion of the ALLHAT results from the calculations of relative risk changed the estimates only slightly (relative risk, 0.73 [CI, 0.60 to 0.87]) and did not introduce heterogeneity into the model.

Table 2. Summary Statistics of the Effectiveness of Lipid-Lowering Therapy in Diabetes*

Study (Reference)	CHD Event Rate, Control Group, n/n	CHD Event Rate, Intervention Group, n/n	Relative Risk for CHD Event (95% CI)	Absolute Risk Reduction in CHD Events	Number Needed To Treat for Benefit
Primary prevention					
AFCAPS/TexCAPS (13)	6/71	4/84	0.56 (0.17 to 1.92)	0.04 (−0.04 to 0.12)	27.1
ALLHAT-LLT (14)	Not reported	Not reported	0.89 (0.71 to 1.10)	Not reported	Not reported
HHS (15, 16)	8/76	2/59	0.32 (0.07 to 1.46)	0.07 (−0.01 to 0.15)	14.0
HPS (17)	367/1976	276/2006	0.74 (0.64 to 0.85)	0.05 (0.03 to 0.07)	20.8
PROSPER (18)†	28/205	32/191	1.23 (0.77 to 1.95)	−0.03 (−0.10 to 0.04)	−32.3
ASCOT-LLA (19)	46/1274	38/1258	0.84 (0.55 to 1.29)	0.01 (−0.01 to 0.02)	169.5
Pooled‡	–	–	0.78 (0.67 to 0.89)	0.03 (0.01 to 0.04)	34.5§
Secondary prevention					
4S (20)	44/97	24/105	0.50 (0.33 to 0.76)	0.23 (0.10 to 0.35)	4.4
CARE (21)	112/304	81/282	0.78 (0.62 to 0.99)	0.08 (0.01 to 0.16)	12.3
HPS (17)	381/1009	325/972	0.89 (0.79 to 1.00)	0.04 (0.00 to 0.09)	23.1
LIPID (22)	88/386	76/396	0.84 (0.64 to 1.11)	0.04 (−0.02 to 0.09)	27.7
LIPS (23)	31/82	26/120	0.53 (0.29 to 0.97)	0.16 (0.03 to 0.29)	6.2
Post-CABG (24)	14/53	9/63	0.53 (0.18 to 1.60)	0.12 (−0.03 to 0.27)	8.2
PROSPER (18)†	31/115	38/112	1.26 (0.85 to 1.87)	−0.07 (−0.19 to 0.05)	−14.3
VA-HIT (25, 26)	116/318	88/309	0.76 (0.57 to 1.01)	0.08 (0.01 to 0.15)	12.5
Pooled‡	–	–	0.76 (0.59 to 0.93)	0.07 (0.03 to 0.12)	13.8§

* 4S = Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS = Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm; CARE = Cholesterol and Recurrent Events trial; CHD = coronary heart disease; HHS = Helsinki Heart Study; HPS = Heart Protection Study; LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease trial; LIPS = Lescol Intervention Prevention Study; Post-CABG = Post-Coronary Artery Bypass Graft trial; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; VA-HIT = Veterans Administration High-Density Lipoprotein Cholesterol Intervention Trial.

† Shepherd J, Blauw GJ, Murphy MB. Personal communication.

‡ Pooled estimates generated by using meta-analysis; for primary prevention, there was no heterogeneity between studies, so a fixed-effects model was used; for secondary prevention, there was substantial between-study heterogeneity ($P = 0.026$), so a random-effects model was used.

§ For primary prevention, the number needed to treat for benefit is for 4.3 years; for secondary prevention, the number needed to treat for benefit is for 4.9 years.

For secondary prevention, there was substantial between-study heterogeneity ($P = 0.03$); thus, we conducted random-effects meta-analyses. The results of these analyses are shown in Table 2 and Figure 2. 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 of those 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 both primary and secondary prevention, we conducted sensitivity analyses excluding the trials with gemfibrozil (Helsinki Heart Study for primary, VA-HIT for secondary); this did not change the estimates of relative risk or absolute risk reduction. For secondary prevention, we also performed a sensitivity analysis excluding the results of 4S, which appears to be an outlier in terms of event rates. This eliminated the heterogeneity seen in the secondary prevention trials and slightly reduced the estimates of effectiveness (relative risk, 0.83 [CI, 0.73 to 0.94]; absolute risk reduction, 0.06 [CI, 0.02 to 0.09]).

DISCUSSION

The principal complication of type 2 diabetes is cardiovascular disease; up to 80% of patients with diabetes will develop or die of some type of major vascular event (27–35). Therefore, the foremost goal of therapy in type 2

diabetes should be preventing cardiovascular disease through optimization of risk factor modification. This includes aggressive treatment of hypertension (7, 36); smoking cessation; aspirin therapy; and, as our review shows, aggressive use of lipid-lowering therapy, particularly with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).

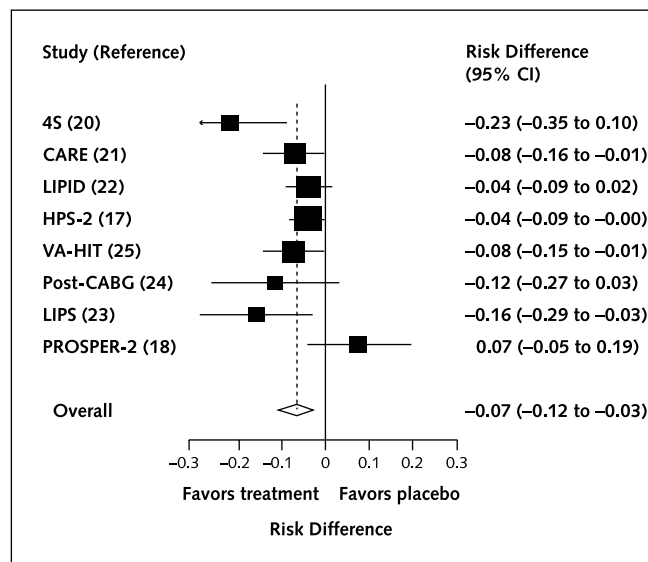
Current medical evidence suggests that lipid-lowering medications lead to about a 22% to 24% reduction in major cardiovascular events in patients with diabetes. Because of small diabetes subgroups in most trials, not all individual trials found benefit. However, the meta-analyses clearly suggest a benefit from using a moderate dose of a statin. There is also evidence of benefit from gemfibrozil, at least among those with low HDL cholesterol levels (<1.03 mmol/L [<40 mg/dL]). Although the relative risk reductions were 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 it (primary prevention). This is a reflection of the fact that the secondary prevention studies universally reported 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. Of note, even among the secondary prevention trials, the absolute risk reduction was largest in the 3 trials

with the highest-risk participants: 4S, which included patients 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 the patients with diabetes, and the observed benefits were quite small or absent in studies in which patients with diabetes had low baseline risk (18, 19). Therefore, we recommend caution in extrapolating the average results found in our 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). Unfortunately, none of the clinical trials conducted subgroup analyses using a multivariable risk prediction tool, a practice that needs to become more common in clinical trial reporting (37, 38).

Given the absolute risk reductions observed in these studies, treatment will probably be cost-effective under most circumstances. However, none of the trials has published a direct analysis of cost-effectiveness from a diabetes subgroup. At least 2 secondary analyses of cost-effectiveness in patients with diabetes have been published, one by the Centers for Disease Control and Prevention using a simulation model based on Framingham data and the United Kingdom Prospective Diabetes Study (8) and another by Grover and colleagues using data from a Canadian cohort (39). The analyses found that lipid-lowering therapy was reasonably cost-effective compared with commonly adopted medical interventions. Overall, the range of cost-effectiveness in the Grover model was from \$4000 to \$40 000 per year of life saved, depending on various patient characteristics, and secondary prevention was more cost-effective than primary prevention (39). The distinction between primary and secondary prevention was not made in the Centers for Disease Control and Prevention model but instead applied to treatment from diabetes onset; the estimate of cost-effectiveness was about \$52 000 per quality-adjusted life-year gained, with substantial variation by age (treatment was most cost-effective in those between 55 and 74 years of age). In comparison, analysis of the cost-effectiveness of hypertension treatment in diabetes was found to be cost-saving in most instances (8).

Although the average benefits of statin therapy for patients with diabetes are fairly clear, there are important issues that cannot be easily answered with the available data. The appropriate target for LDL cholesterol levels remains, at best, poorly defined. While the National Cholesterol Education Panel (NCEP) guidelines state that patients with diabetes should be treated to a target LDL cholesterol level of 2.59 mmol/L (100 mg/dL) and that drug therapy should be started if LDL cholesterol levels exceed 3.36 mmol/L (>130 mg/dL) (40), currently available clinical trial data do not firmly support this specific approach. Current trials either did not set specific LDL cholesterol target levels or used different targets than those

Figure 2. Meta-analysis of the absolute risk reduction of lipid-lowering as secondary prevention in patients with diabetes.



The meta-analysis was done by using a random-effects model because of between-study heterogeneity ($P = 0.026$). 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events trial; HPS-2 = Heart Protection Study (secondary prevention arm); LIPID = Long-term Intervention with Pravastatin in Ischemic Disease trial; LIPS = Lescol Intervention Prevention Study; Post-CABG = Post-Coronary Artery Bypass Graft trial; PROSPER-2 = Prospective Study of Pravastatin in the Elderly at Risk (secondary prevention arm); VA-HIT = Veterans Administration High-Density Lipoprotein Cholesterol Intervention Trial.

commonly proposed (Table 2). While the achieved LDL cholesterol levels in trials are consistently under 3.1 mmol/L (<120 mg/dL), different studies have found differing benefit for lower target levels. For example, the CARE study found that if the baseline LDL cholesterol level was less than 3.23 mmol/L (<125 mg/dL), then there was no benefit to lipid-lowering therapy, at least in the general population (21). In contrast, no such thresholds were identified in the LIPID study or in the HPS (17, 22). Indeed, the HPS, which is the largest of the studies and included the most patients with diabetes, showed that there was a consistent, approximately 25% relative risk reduction and a 5% to 7% absolute risk reduction in cardiovascular event rates regardless of starting LDL cholesterol levels, even among those whose starting LDL cholesterol levels were at or near the NCEP's stated target of 2.59 mmol/L (100 mg/dL). This suggests that empirical use of statins for diabetic persons with average or above average cardiovascular risk is much more important than the baseline or target LDL cholesterol level. It could be argued that there is no strict definition of hyperlipidemia in patients with type 2 diabetes, since nearly the entire population qualifies for lipid-lowering treatment.

Although treatment goals remain somewhat poorly defined by randomized trials, an argument could be made for

an LDL cholesterol level goal as low as 1.81 to 1.94 mmol/L (70 to 75 mg/dL), based on cohort analyses. However, such conclusions would be speculative at this time because most trials lack specific target lipid levels and cohort studies largely examine naturally occurring LDL cholesterol levels rather than treatment-induced levels. Even if this speculation is found to be accurate, the curvilinear relationship between LDL cholesterol levels and cardiac risk (41) would suggest that the incremental absolute benefit of such a strategy would be relatively low and that the number needed to treat for benefit and the cost-effectiveness of treatment are likely to be much less favorable, especially in those with average cardiovascular risk (42). Furthermore, it is not clear that target LDL cholesterol levels of 1.81 to 1.94 mmol/L (70 to 75 mg/dL) are commonly achievable in practice. Indeed, the studies reviewed here did not achieve LDL cholesterol levels below 2.3 mmol/L (<89 mg/dL), even the few that had statin dose titration or used multiple agents (Table 1).

Even setting an LDL cholesterol target of less than 2.59 mmol/L (<100 mg/dL) rather than simply recommending moderate doses of statins for most or all patients with type 2 diabetes is difficult to justify from the literature. Not only is clinical trial evidence lacking to support titration of therapy to reach this goal, but statins have potential non-lipid-related effects. For example, statins may modulate cardiovascular risk by reducing inflammation, by stabilizing existing plaque, and by improving endothelial function (43–46). One could easily speculate that if statins do have a lipid-independent effect on cardiovascular risk, then wide-scale use of at least moderate doses of statins may be more beneficial than dose titration based on LDL cholesterol levels. However, the importance of these lipid-independent benefits has not been established in clinical trials, and whether other markers (such as C-reactive protein or nitrotyrosine levels) may be better indicators for use and titration of statins remains unclear (47, 48).

Perhaps the best conclusion to be drawn from the currently available data (particularly that from the HPS) is that most patients with diabetes should be taking at least moderate dosages of statins (for example, simvastatin, 40 mg/d; pravastatin, 40 mg/d; lovastatin, 40 mg/d; atorvastatin, 20 mg/d; or an equivalent dose of another statin). Given the absence of clinical trial data on the subject, the decision of whether to further increase statin doses or to use combination lipid-lowering treatment titrated on the basis of LDL cholesterol levels should be left to individual clinicians and patients. Our appraisal of the literature suggests that one could equally advocate for empirical maximization of statin dose as tolerated.

For the reasons mentioned previously, we also do not feel that the evidence is sufficient to make strong recommendations for primary prevention therapy for people with diabetes who have relatively low cardiovascular risk. While overall risk is elevated in patients with diabetes, the relatively low event rates in ASCOT-LLA show that some pa-

tients with diabetes are at low risk. This trial had an event rate of only 3.6% over 3.3 years in the control group of patients with diabetes, which is below the 2% per year guideline used to recommend treatment in the NCEP (19). Finally, we strongly advocate reanalysis of the lipid-lowering trials reviewed here using multivariable risk-stratification prediction tools. With such analyses, existing data could shed considerable light on the issue of relative and absolute benefits for higher-risk versus lower-risk patients and could allow more accurate individual tailoring of therapy (37, 38).

In addition, the current literature suggests that statins are extremely safe. While discontinuation and nonadherence rates in clinical trials are reasonably high ($\geq 15\%$ in many cases), rates of discontinuation typically are not different from those of placebo. Rates of elevated liver or muscle enzyme levels did not differ between 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 creatinine kinase levels were 0.3% in the simvastatin group and 0.2% in the placebo group (17). Neither of these differences were statistically significant. Similarly, among the 5804 patients in PROSPER, only 1 in each group had an alanine aminotransferase or aspartate aminotransferase level more than 3 times the upper limit of normal (18). In addition, there were no cases of rhabdomyolysis and 36 cases of myalgia in the pravastatin group compared with 32 in the placebo group (17, 18, 49, 50). Considering the safety of these drugs, routine monitoring of liver or muscle enzymes is probably not warranted unless patients have symptoms, have liver enzyme abnormalities at baseline, or are taking drugs that interact with the statins to increase the risk for adverse events. This simplifies and reduces the cost of treatment and would be similar, for example, to simply prescribing a daily aspirin for a patient with diabetes (51).

Another possible exception to the “statins for all” rule in patients with diabetes is in those with low HDL and LDL cholesterol levels. These patients may benefit more from gemfibrozil than from a statin, although there are no head-to-head comparisons of the drugs (25). However, unlike therapy with statins, the benefits of gemfibrozil therapy may be attenuated in patients with very low baseline LDL cholesterol levels of around 2.59 mmol/L (100 mg/dL). In patients with LDL cholesterol levels above 2.59 mmol/L (>100 mg/dL) and low HDL cholesterol levels, combination therapy with both a statin and gemfibrozil could be considered. However, there are as yet no efficacy data on combination therapy, and the risks of treatment, while modest, are elevated compared with those for single-agent therapy (52). Some of these questions will be better addressed by future studies that are comparing dose–response effects and the effect of combinations of lipid-lowering therapy on clinical outcomes.

Given the markedly elevated risk for cardiovascular events in people with type 2 diabetes, aggressive management of lipids provides substantial benefit, at least to the average patient. The use of statins should be nearly universal in this population. The current literature offers stronger support for empirical use of at least moderate doses of statins than it does for targeting specific LDL cholesterol levels. An argument can be made for using gemfibrozil as first-line therapy for patients with low HDL cholesterol levels and moderately low LDL cholesterol levels. Future studies should evaluate the relative effectiveness of specific strategies, such as different LDL cholesterol targets versus different doses of empirical statin therapy and combination therapy, and should also consider the potential effects of statins beyond lipid lowering.

Note added in proof: As this review went to press, a study of intensive lipid lowering in patients with acute coronary syndromes demonstrated the superiority of 80 mg of atorvastatin over 40 mg of pravastatin (Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004; Mar 8 [Epub ahead of print] [PMID: 15007110]). This study evaluated secondary prevention in a highly selected population and has limited statistical power for analyses of the diabetes subgroup. The implications of the study for most patients with diabetes is unclear; however, more aggressive lipid-lowering therapy should be considered for patients admitted with acute coronary syndromes.

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References

- Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, et al. The continuing increase of diabetes in the US [Letter]. *Diabetes Care*. 2001;24:412. [PMID: 11213906]
- National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2000. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2002.
- Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR,

- et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care*. 1998;21:518-24. [PMID: 9571335]
- Diabetes in America. 2nd ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995.
- Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998; 352:837-53. [PMID: 9742976]
- Economic consequences of diabetes mellitus in the U.S. in 1997. American Diabetes Association. *Diabetes Care*. 1998;21:296-309. [PMID: 9539999]
- Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: blood pressure goals, choice of agents, and setting priorities in diabetes care. *Ann Intern Med*. 2003;138:593-602. [PMID: 12667032]
- Cost-effectiveness of intensive glycaemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. *JAMA*. 2002;287: 2542-51. [PMID: 12020335]
- Feingold KR, Grunfeld C, Pang M, Doerrler W, Krauss RM. LDL subclass phenotypes and triglyceride metabolism in non-insulin-dependent diabetes. *Arterioscler Thromb*. 1992;12:1496-502. [PMID: 1450181]
- Barrett-Connor E, Grundy SM, Holdbrook MJ. Plasma lipids and diabetes mellitus in an adult community. *Am J Epidemiol*. 1982;115:657-63. [PMID: 7081197]
- Sackett DL. Evidence-Based Medicine: How To Practice and Teach EBM. 2nd ed. New York: Churchill Livingstone; 2000.
- Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301-7. [PMID: 7566020]
- Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615-22. [PMID: 9613910]
- Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002; 288:2998-3007. [PMID: 12479764]
- Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237-45. [PMID: 3313041]
- Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care*. 1992;15:820-5. [PMID: 1516498]
- MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22. [PMID: 12114036]
- Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623-30. [PMID: 12457784]
- Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149-58. [PMID: 12686036]
- Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care*. 1997;20:614-20. [PMID: 9096989]
- Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335:1001-9. [PMID: 8801446]
- Prevention of cardiovascular events and death with pravastatin in patients

- with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med*. 1998;339:1349-57. [PMID: 9841303]
23. Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;287:3215-22. [PMID: 12076217]
 24. Hoogwerf BJ, Waness A, Cressman M, Canner J, Campeau L, Domanski M, et al. Effects of aggressive cholesterol lowering and low-dose anticoagulation on clinical and angiographic outcomes in patients with diabetes: the Post Coronary Artery Bypass Graft Trial. *Diabetes*. 1999;48:1289-94. [PMID: 10342818]
 25. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341:410-8. [PMID: 10438259]
 26. Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med*. 2002;162:2597-604. [PMID: 12456232]
 27. Harris MI. Epidemiology of diabetes mellitus among the elderly in the United States. *Clin Geriatr Med*. 1990;6:703-19. [PMID: 2224742]
 28. Meigs JB, Singer DE, Sullivan LM, Dukes KA, D'Agostino RB, Nathan DM, et al. Metabolic control and prevalent cardiovascular disease in non-insulin-dependent diabetes mellitus (NIDDM): The NIDDM Patient Outcome Research Team. *Am J Med*. 1997;102:38-47. [PMID: 9209199]
 29. Morrish NJ, Stevens LK, Fuller JH, Keen H, Jarrett RJ. Incidence of macrovascular disease in diabetes mellitus: the London cohort of the WHO Multinational Study of Vascular Disease in Diabetics. *Diabetologia*. 1991;34:584-9. [PMID: 1936662]
 30. Wingard DL, Barrett-Connor EL, Scheidt-Nave C, McPhillips JB. Prevalence of cardiovascular and renal complications in older adults with normal or impaired glucose tolerance or NIDDM. A population-based study. *Diabetes Care*. 1993;16:1022-5. [PMID: 8359095]
 31. de Grauw WJ, van de Lisdonk EH, van den Hoogen HJ, van Weel C. Cardiovascular morbidity and mortality in type 2 diabetic patients: a 22-year historical cohort study in Dutch general practice. *Diabet Med*. 1995;12:117-22. [PMID: 7743757]
 32. Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. *Diabetes*. 1974;23:105-11. [PMID: 4359625]
 33. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA*. 1979;241:2035-8. [PMID: 430798]
 34. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB. Mortality among diabetics in a national sample. *Am J Epidemiol*. 1988;128:389-401. [PMID: 3394705]
 35. Krolewski AS, Czyzyk A, Janeczko D, Kopczynski J. Mortality from cardiovascular diseases among diabetics. *Diabetologia*. 1977;13:345-50. [PMID: 913925]
 36. Snow V, Weiss KB, Mottur-Pilson C. The evidence base for tight blood pressure control in the management of type 2 diabetes mellitus. *Ann Intern Med*. 2003;138:587-92. [PMID: 12667031]
 37. Rothwell PM. Can overall results of clinical trials be applied to all patients? *Lancet*. 1995;345:1616-9. [PMID: 7783541]
 38. Vijan S, Kent DM, Hayward RA. Are randomized controlled trials sufficient evidence to guide clinical practice in type II (non-insulin-dependent) diabetes mellitus? *Diabetologia*. 2000;43:125-30. [PMID: 10672454]
 39. Grover SA, Coupal L, Zowall H, Dorais M. Cost-effectiveness of treating hyperlipidemia in the presence of diabetes : who should be treated? *Circulation*. 2000;102:722-7. [PMID: 10942738]
 40. Executive 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*. 2001;285:2486-97. [PMID: 11368702]
 41. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256:2823-8. [PMID: 3773199]
 42. Shepherd J. Resource management in prevention of coronary heart disease: optimising prescription of lipid-lowering drugs. *Lancet*. 2002;359:2271-3. [PMID: 12103306]
 43. Sotiriou CG, Cheng JW. Beneficial effects of statins in coronary artery disease—beyond lowering cholesterol. *Ann Pharmacother*. 2000;34:1432-9. [PMID: 11144702]
 44. Rosenson RS. Non-lipid-lowering effects of statins on atherosclerosis. *Curr Cardiol Rep*. 1999;1:225-32. [PMID: 10980846]
 45. Kinlay S, Selwyn AP. Effects of statins on inflammation in patients with acute and chronic coronary syndromes. *Am J Cardiol*. 2003;91:9B-13B. [PMID: 12615293]
 46. Liao JK. Beyond lipid lowering: the role of statins in vascular protection. *Int J Cardiol*. 2002;86:5-18. [PMID: 12243846]
 47. Shishehbor MH, Aviles RJ, Brennan ML, Fu X, Goormastic M, Pearce GL, et al. Association of nitrotyrosine levels with cardiovascular disease and modulation by statin therapy. *JAMA*. 2003;289:1675-80. [PMID: 12672736]
 48. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347:1557-65. [PMID: 12432042]
 49. Smith CC, Bernstein LI, Davis RB, Rind DM, Shmerling RH. Screening for statin-related toxicity: the yield of transaminase and creatine kinase measurements in a primary care setting. *Arch Intern Med*. 2003;163:688-92. [PMID: 12639201]
 50. Gotto AM Jr. Safety and statin therapy: reconsidering the risks and benefits [Editorial]. *Arch Intern Med*. 2003;163:657-9. [PMID: 12639194]
 51. Kmietowicz Z. Statins are the new aspirin, Oxford researchers say. *BMJ*. 2001;323:1145. [PMID: 11711389]
 52. Xydakis AM, Ballantyne CM. Combination therapy for combined dyslipidemia. *Am J Cardiol*. 2002;90:21K-29K. [PMID: 12467937]

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