Review

The Role of Lipid-lowering Therapy in Preventing Coronary Heart Disease in Patients with Type 2 Diabetes

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ABSTRACT

Coronary heart disease (CHD) is the most common cause of death among diabetic patients. The increased risk of CHD in type 2 diabetes is due, in part, to lipid abnormalities often present in the diabetic patient. Diabetic dyslipidemia is characterized by elevated triglycerides, low high-density lipoprotein cholesterol (HDL-C), and an increased preponderance of small, dense low-density lipoprotein cholesterol (LDL-C) particles. Current guidelines for the prevention of coronary heart disease in diabetic patients identify elevated LDL-C as the primary target of lipid-lowering therapy, and recommend statins as the first-line treatment for diabetic dyslipidemia. This review evaluates the large statin trials that have included diabetic patients, and discusses the role of combination therapy in managing dyslipidemia in diabetic patients.

Key words: lipids, statins, diabetes mellitus, cardiovascular disease

Introduction

Coronary heart disease (CHD) is the most common cause of death in diabetic patients.[1,2] The increased risk of CHD in type 2 diabetes is due to a constellation of risk factors, including dyslipidemia. Diabetic dyslipidemia is characterized by elevated triglyceride levels and decreased high-density lipoprotein cholesterol (HDL-C) levels, with low-density lipoprotein cholesterol (LDL-C) levels that are not different from nondiabetic individuals. However, diabetic patients typically have a preponderance of smaller, denser, and more atherogenic LDL-C particles. Projections made from a United States population study estimate that over 70% of patients with type 2 diabetes do not reach their LDL-C target of <100 mg/dL.[3] Furthermore, more than half of men and more than two-thirds of women with diabetes have low HDL-C, and more than half have elevated levels of triglycerides.[3] Only 3% of patients with type 2 diabetes reach their American Diabetes Association (ADA) targets for all 3 lipid parameters.[3] Thus, improved lipid management is essential in this high-risk group.

Treatment of Dyslipidemia in Patients with Type 2 Diabetes

Elevated LDL-C is recognized as the primary target of lipid-lowering therapy in diabetic patients[4,5] and early trials, such as the Scandinavian Simvastatin Survival Study (4S),[6] the Cholesterol And Recurrent Events (CARE) trial,[7] and the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study[8] were the first to show the benefit of statin therapy in the secondary prevention of CHD in diabetic patients. The Heart Protection Study (HPS) included almost 6,000 diabetic patients, many of whom had no history of vascular disease.[9] Compared with placebo, treatment with simvastatin 40 mg reduced the risk of major cardiovascular events by 22% in this mixed cohort of diabetic patients. Among 2,912 primary prevention patients with diabetes a 33% reduction in cardiovascular events was seen, providing evidence for statin therapy even in diabetic patients without overt CHD.[9] The benefit of Simvastatin in HPS extended to individuals whose LDL-C was <100 mg/dL, suggesting that in high-risk individuals statin therapy can significantly reduce risk independent of baseline LDL-C levels. The Collaborative Atorvastatin Diabetes Study (CARDS) was the first trial to be conducted exclusively in patients with type 2 diabetes without CHD. The CARDS was stopped 2 y earlier than anticipated, when a significant benefit of Atorvastatin 10 mg compared with placebo became apparent after a median follow-up period of 3.9 y. Lowering LDL-C with Atorvastatin reduced the relative risk of a first cardiovascular event by 37% in patients with diabetes who, by contemporary guidelines, were not considered to have elevated LDL-C.[10] Based on these findings, the CARDS investigators suggested that patients with type 2 diabetes should be treated according to their high-risk status rather than their LDL-C level.[10]

Although HPS and CARDS demonstrated significant benefits with low- to moderate-dose statin therapy in diabetic patients without CHD, other primary prevention trials have failed to demonstrate a significant benefit of statin therapy in reducing the incidence of CHD in lower-risk diabetic patients. In the lipid-lowering arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid-Lowering Treatment (ALLHAT-LLT), 3,638 patients

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with type 2 diabetes were randomized to Pravastatin 40 mg or usual care. Although fewer diabetic patients in the Pravastatin group experienced CHD events, there was no significant treatment effect, likely due to a high rate of open-label statin use in the usual care group.[11] In the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin-dependent diabetes mellitus (ASPEN), the 10% reduction in cardiovascular events observed with Atorvastatin 10 mg versus placebo was not significant.[12] The study was designed as a secondary prevention study, but due to evolving treatment guidelines during the period of enrollment the study protocol was altered to allow patients without CHD to enter the study, which may have led to insufficient power to detect a treatment difference. In addition, the high statin drop-in rate in the placebo group may also explain why no treatment benefit was seen in this study. A prespecified subanalysis of the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) showed that, compared with placebo, Atorvastatin 10 mg was associated with a nonsignificant 16% reduction in risk of the primary endpoint of fatal CHD and nonfatal myocardial infarction (MI) in hypertensive diabetic patients with no history of CHD.[13] However, the overall lipid-lowering arm of ASCOT was stopped 2 y earlier than anticipated due to a significant benefit of Atorvastatin versus placebo, which meant that there were fewer primary events than projected in the diabetic subanalysis and, therefore, insufficient power to detect a treatment difference. Nevertheless, there was no heterogeneity of treatment effect between diabetic and nondiabetic patients, and an extended endpoint of all cardiovascular events showed a significant 23% risk reduction with Atorvastatin 10 mg, compared with placebo.[13]

Trials such as LIPID, HPS, and CARDS established the benefit of low- to moderate-dose statin therapy in the primary and secondary prevention of CHD in diabetic patients. More recent trials have shown that high-dose statin therapy further reduces cardiovascular risk compared with lower-dose statin therapy. The Treating to New Targets (TNT) trial examined the benefit of lowering LDL-C well below 100 mg/dL with Atorvastatin 80 mg versus more moderate lipid lowering with Atorvastatin 10 mg to prevent major cardiovascular events in patients with CHD. Intensive treatment with Atorvastatin 80 mg was associated with a 27% reduction in LDL-C over that achieved with Atorvastatin 10 mg, and reduced the relative risk of a major cardiovascular event by 22% compared with treatment with Atorvastatin 10 mg.[14] A post hoc analysis of the TNT trial demonstrated similar relative reductions in the risk of major cardiovascular events with intensive Atorvastatin treatment in a subpopulation of 1,501 patients with diabetes.[15] The benefit of intensive Atorvastatin treatment has also been observed in patients with acute coronary syndromes. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study compared intensive treatment with Atorvastatin 80 mg to moderate lipid-lowering treatment with Pravastatin 40 mg in the prevention of cardiovascular events in patients who had been hospitalized for MI or unstable angina in the previous 10 d. A post hoc analysis of 978 patients with diabetes demonstrated that after only 2 y, high-dose Atorvastatin reduced the relative risk of acute cardiac events by 25%.[16]

Despite differences in the patient populations and designs of the statin trials in type 2 diabetes, the totality of evidence from both primary and secondary prevention trials support the use of statin therapy in patients with diabetes (Table 1). Furthermore, recent meta-analyses of patients with diabetes have demonstrated the benefit of achieving low LDL-C with statins in the prevention of cardiovascular events, both in primary and secondary prevention.[17,18]

Fibrates lower triglycerides and raise HDL-C levels, but have only modest effects in lowering LDL-C. In post hoc analyses, fibrates have been shown to reduce cardiovascular events in patients with diabetes.[20,21] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a large, randomized, placebo-controlled trial conducted in 9,795 patients with type 2 diabetes that examined the effect of fibrate treatment in preventing CHD events.[22] Overall, there was a nonsignificant 11% reduction in the primary endpoint of CHD death and nonfatal MI, and a significant 11% reduction in total cardiovascular events, largely due to reductions in nonfatal MI and coronary revascularization. The FIELD study did not directly compare the effects of a statin versus a fibrate, and there was a high statin drop-in rate during the study. Nonetheless, it was concluded that the data do not provide sufficient evidence to support a change from the current guidelines recommending statins as first-line lipid-lowering therapy in type 2 diabetes.[22]

Mechanisms by Which Statins Prevent Cardiovascular Events

Diabetic dyslipidemia is characterized by a preponderance of small, dense LDL particles, elevated levels of triglyceride and triglyceride-rich remnant lipoproteins, and low levels of HDL-C. The primary mechanism by which statins prevent cardiovascular disease is by lowering levels of LDL-C, but statins also have anti-inflammatory properties and have favorable effects on other lipoproteins in the diabetic patient.

In the New Atorvastatin Starting Doses: A Comparison (NASDAC) study, a post hoc subanalysis of almost 200 patients with hypertriglyceridemia (triglycerides $\geq$200 mg/dL), LDL particle size increased with each dose of Atorvastatin.[23] Higher doses more favorably changed particle size and concentration than did lower doses. In addition more than 80% of patients receiving Atorvastatin 80 mg achieved normal levels of triglyceride-rich lipoproteins.[23] Several statin trials have demonstrated modest increases in HDL-C

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TABLE 1: Clinical outcome trials of statin therapy in diabetic patients for the primary and secondary prevention of CHD events

		Patient baseline characteristics								CHD event rate[a] (%)			
Study	Statin	Cardiovascular history	Patient number	Age (y)	% men	Fasting glucose (mg/dL)	LDL-C (mg/dL)	Median follow-up (years)	LDL-C Reduction (versus placebo) (%)	Placebo	statin	Relative risk reduction[a] (%)	P-value
Secondary prevention													
4S[6]	Simvastatin 20–40 mg	MI or angina	202	60	78	175	186	5.3	−36	45.4	22.9	−55	0.002
4S[19]	Simvastatin 20–40 mg	MI or angina	483	59	84	153	187	5.4	−38	37.5	23.5	−42	0.001
CARE[7]	Pravastatin 40 mg	MI	586	61	80	149	136	4.8	−27	20.4	17.7	−13	ns
LIPID[8]	Pravastatin 40 mg	MI or hospitalization for unstable angina	1077	64	81	139	143	5.6	−27	23.4	19.6	−19	ns
HPS[9]	Simvastatin 40 mg	MI or other CHD	1981	62[b]	70[b]	—	124[b]	4.8[b]	−27	21.0	17.4	−17	<0.05
ASPEN[12]	Atorvastatin 10 mg	MI or interventional procedure	505	63	82	—	113	4.0	−26	12.6	8.3	−34	ns
TNT[15]	Atorvastatin 80 mg	MI, angina, or revascularization	1501	63	73	154	96	4.9	−16[c]	12.9[c]	10.6	−19[c]	ns
PROVE IT-TIMI 22[16]	Atorvastatin 80 mg	MI or unstable angina in previous 10 d	978	60	72	—	101	2.0	−26[d]	26.6[d]	21.1	−25[d]	0.03

TABLE 1: (*Continued*)

Study	Statin	Patient baseline characteristics: Cardiovascular history	Patient number	Age (y)	% men	Fasting glucose (mg/dL)	LDL-C (mg/dL)	Median follow-up (years)	LDL-C Reduction (versus placebo) (%)	CHD event rate[a] (%): Placebo	CHD event rate[a] (%): Statin	Relative risk reduction[a] (%)	P-value
Primary prevention													
ALLHAT-LLT[11]	Pravastatin 40 mg	Hypertension + ≥ 1 other CHD risk factor	3638	—	—	—	—	4.8[e]	−16.7[e]	—	—	−11	ns
HPS[9]	Simvastatin 40 mg	No history of arterial disease	2912	62[b]	70[b]	—	124[b]	4.8[b]	−29	6.5	3.7	−43	<0.05
CARDS[10]	Atorvastatin 10 mg	Hypertension, retinopathy, albuminuria, or smoking	2838	62	68	179	117	3.9	−40	5.5	3.6	−36	<0.05
ASCOT-LLA[13]	Atorvastatin 10 mg	Hypertension + other CV risk factors	2532	64	76	156	128	3.3	−27	3.6	3.0	−16	ns
ASPEN[12]	Atorvastatin 10 mg	No previous MI or interventional procedure	1905	60	62	—	114	4.0	−30	3.6	2.9	−19	ns

[a]CHD event rate and relative risk reduction refers to CHD death+nonfatal MI for all studies except 4S (CHD death, nonfatal MI, and resuscitated cardiac arrest), ASPEN (fatal and nonfatal MI), TNT (CHD death, nonfatal nonprocedure-related MI, and resuscitated cardiac arrest), PROVE IT–TIMI 22 (death, MI, and unstable angina requiring hospitalization), and CARDS (MI, CHD death, unstable angina, and resuscitated cardiac arrest). [b]HPS baseline data are for all patients with diabetes (irrespective of presence or absence of CVD). [c]Comparator group in the TNT study was Atorvastatin 10 mg. [d]Comparator group in the PROVE IT–TIMI 22 study was pravastatin 40 mg. [e]Median follow-up and LDL-C reduction for the overall ALLHAT lipid-lowering trial (n = 10,355); comparator group was under usual care. *Abbreviations*: ALLHAT-LLT = antihypertensive and lipid-lowering treatment to prevent heart attack trial-lipid-lowering treatment; ASCOT-LLA = anglo-scandinavian cardiac outcomes trial-lipid lowering arm; ASPEN = atorvastatin study for prevention of coronary heart disease endpoints in non-insulin-dependent diabetes mellitus; CARE = cholesterol and recurrent events; CARDS = collaborative atorvastatin diabetes study; CHD = coronary heart disease; HPS = heart protection study; LDL-C = low-density lipoprotein cholesterol; LIPID = long-term intervention with pravastatin in ischaemic disease; MI = myocardial infarction; PROVE IT-TIMI 22 = pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22; TNT = treating to new targets.

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across a range of doses, particularly in the most protective HDL-2 subclass,[23] and a meta-analysis has revealed that for every 1 mg/dL increase in HDL-C there is an estimated 2%–3% decrease in cardiovascular risk, independent of other risk factors including LDL-C.[24] Thus, the benefit of raising HDL-C and lowering LDL-C and triglycerides may be additive.

Statins have been shown to have anti-inflammatory properties. In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study patients who achieved the greatest reduction in LDL-C benefited from a reduction in atherosclerotic progression; however, atherosclerotic regression was seen only in patients who achieved the greatest reduction in C-reactive protein (CRP), a marker of inflammation.[25] This led the REVERSAL authors to conclude that the role of CRP reduction in the prevention of coronary atherosclerosis was independent of the reduction in LDL-C.[25] Evidence also suggests that statins reduce CRP levels in a dose-dependent manner, with one small clinical trial consisting of 186 diabetic patients reporting a 47% reduction in CRP with Atorvastatin 80 mg, compared with a 15% reduction with Atorvastatin 10 mg.[26] Thus, high-dose statin therapy may be beneficial in CHD prevention independent of its effect on LDL-C lowering.

Combination Lipid-lowering Therapy in Managing Residual Cardiovascular Risk

Despite intensive statin therapy, many patients with type 2 diabetes remain at residual risk of cardiovascular events.[15,16] Therefore, additional lipid-lowering strategies are required in this high-risk group.[16] The American Diabetes Association (ADA), American Heart Association (AHA), and National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines for CHD prevention all recognize the potential for combination therapy in treating diabetic patients with high triglycerides ($\geq$200 mg/dL) or low HDL ($<$40 mg/dL for men and $<$50 mg/dL for women), and recommend the addition of niacin or fibrates to statin therapy in order to improve the entire lipid profile and lower the risk of CHD further.[1,2,4,5]

One option for patients with type 2 diabetes may be the combination of a fibrate with statin therapy. Statin-fibrate combination therapy has been demonstrated to modify the whole lipid profile of patients with diabetes.[27,28] However, there is limited clinical trial data that demonstrates additional prevention of cardiovascular events compared with statin therapy alone. In one small clinical trial, combination therapy of Atorvastatin and fenofibrate resulted in most patients with type 2 diabetes achieving their HDL-C, triglyceride, and LDL-C targets.[28] Another small statin-fibrate combination trial demonstrated that, compared with either monotherapy, combination treatment with Simvastatin and Bezafibrate further improved the lipid profile and reduced the cardiovascular event rate in patients with type 2 diabetes.[27] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study is an ongoing, large, clinical endpoints trial that will evaluate the efficacy and safety of Simvastatin-Fenofibrate combination therapy in patients with type 2 diabetes. Although ACCORD has not yet been completed, limited existing clinical trial data suggests that statin-fibrate combination therapy may be an efficacious treatment for patients with type 2 diabetes.

There are more than 60 case reports published to date of serious myopathy when Gemfibrozil was combined with a statin, compared with only 2 reported cases of serious myopathy with Fenofibrate in combination with a statin.[29] The reason for the much greater propensity for Gemfibrozil to increase the risk of myopathy in combination with a statin, compared with Fenofibrate, is likely due to the difference in pharmacokinetic interactions of the 2 fibrates. Gemfibrozil interferes with the renal excretion of lipophilic statins through inhibition of glucuronidation, leading to higher serum levels of these statins and a higher risk of severe myopathy.[29] Thus, combination therapy involving Gemfibrozil may not be a suitable option for treating dyslipidemia in diabetic patients, and the use of Fenofibrate should be considered instead.

Niacin is the most effective agent currently available for increasing HDL-C, and is recommended for the treatment of isolated low HDL-C.[4] Small trials have demonstrated the beneficial effect of statin and Niacin in combination on changes in the lipid profile and in reducing cardiovascular events. The HDL-Atherosclerosis Treatment Study (HATS) found that, compared with placebo, Simvastatin-Niacin combination therapy improved each component of the lipid profile, reversed the progression of coronary atherosclerosis, and reduced the incidence of cardiovascular events in patients with CHD.[30] Patients treated for 3 y with the combination of Simvastatin and Niacin had a 90% lower rate of major cardiovascular events compared with the placebo group. Although HATS did not directly compare statin alone versus statin-niacin therapy, the clinical and angiographic benefits of combination lipid-lowering therapy were greater than what would have been expected from statin therapy alone. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 3 (ARBITER 3) study was a small clinical trial that enrolled patients with CHD and investigated the effect of statin-Niacin in combination versus statin alone on carotid intima-media thickness (CIMT), a marker of atherosclerosis.[31] After 12–24 mo, a subgroup of 62 patients with insulin resistance (type 2 diabetes or the metabolic syndrome) showed an improvement in HDL-C and significant regression in CIMT, relative to baseline, compared with statin therapy alone.[31] Despite the apparent benefit of statin-Niacin therapy in improving the lipid profile and slowing the progression of atherosclerosis in patients with CHD, no large clinical trials have been completed

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continued

TABLE 2: Cardiovascular disease management guidelines for diabetic patients

Guidelines	Primary lipid targets in diabetic patients	Treatment recommendations	Secondary lipid targets in diabetic patients
NCEP ATP III[4]	Patients without CVD	Intensity of therapy should be sufficient to achieve a 30%–40% reduction in LDL-C	For patients with triglycerides ≥ 200 mg/dL a non-HDL-C goal of≤130 mg/dL is recommended
	LDL-C <100 mg/dL Patients with CVD Optional LDL-C goal <70 mg/dL		
AHA/ACC[5]	Patients without CVD		For patients with triglycerides≥200 mg/dL a nonHDL-C goal of <130 mg/dL is recommended
	LDL-C <100 mg/dL Patients with CVD Reasonable LDL-C goal <70 mg/dL		
ADA[2]	Patients without CVD	For patients aged over 40 y, statin therapy to achieve an LDL-C reduction of 30%–40%	Triglycerides <150 mg/dL
	LDL-C <100 mg/dL		HDL-C >40 mg/dL (>50 mg/dL for women)
	Patients with CVD	All patients should be treated with a statin to achieve an LDL-C reduction of 30%–40%	
	Optional LDL-C goal <70 mg/dL		

Abbreviations: ADA = american diabetes association; AHA = american heart association; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NCEP ATP = National Cholesterol Education Program Adult Treatment Panel

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that demonstrate any benefit of this treatment in reducing cardiovascular events, although the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM HIGH) trial is currently investigating this. The main side effects of Niacin are skin flushing and the deterioration of glycemic control in patients with insulin resistance or diabetes. However, in clinical trials, the drop-out rate due to flushing is usually less than 10%, and for diabetic patients with good glycemic control, Niacin can be safely used, though glycemic control needs to be closely monitored.[30]

Ezetimibe is the first available selective cholesterol absorption inhibitor. Statin-Ezetimibe combination therapy has been shown to provide significantly greater improvements in the lipid profile of patients with hypercholesterolemia compared with statin therapy alone. Coadministration of Ezetimibe with a statin significantly reduced levels of LDL-C and triglycerides and resulted in modest elevations of HDL-C compared with statin monotherapy.[32] Further, Ezetimibe plus statin treatment was well tolerated, with a safety profile similar to that of statin monotherapy and placebo.[32] Ezetimibe treatment may be of most use when LDL-C is not at goal with maximal statin dose. However, no clinical outcomes data currently exist to support the use of Ezetimibe in preventing CHD events.

Lipid-lowering Guidelines for Patients with Type 2 Diabetes

The ADA, AHA, and NCEP ATP III have all released similar guidelines for lipid management in patients with type 2 diabetes[1,2,4,5] (Table 2). Although it is recommended that therapeutic lifestyle changes, such as improvements in diet and increased physical activity, be initiated in all patients with type 2 diabetes, most patients remain at significant risk of CHD and require lipid-lowering therapy.[1,2,4,5] Low-density lipoprotein cholesterol is currently the primary target of lipid-lowering therapy and statins are the drugs of choice to lower LDL-C.

For simplicity, all patients with diabetes are classified as being CHD risk equivalents according to the most recent NCEP ATP III update, and have an LDL-C goal of <100 mg/dL.[4] Patients with both CHD and type 2 diabetes are recognized as being at very high risk of recurrent cardiovascular events, and these patients have an optional LDL-C goal of <70 mg/dL.[4] Elevated triglycerides and low HDL-C are independent CHD risk factors and have been identified as secondary targets of lipid-lowering therapy, after the primary target of LDL-C has been met. For high-risk patients who have elevated triglycerides (≥ 200 mg/dL in ATP III and AHA/ACC, >150 mg/dL in ADA) or low HDL-C levels (<40 mg/dL for men, <50 mg/dL for women), guidelines state that addition of a fibrate or Niacin to LDL-lowering therapy should be considered.[1,2,4,5]

To reduce the risk of CHD in patients with type 2 diabetes, physicians must initiate early and effective lipid-lowering therapy. Statin therapy is often underutilized in clinical practice, and when used the doses of statins are often too low to achieve the aggressive targets recommended for patients with diabetes. Dyslipidemia can be effectively managed through pharmacologic lipid-lowering therapy, and adherence to the national guidelines will reduce the risk of CV events in our diabetic patients.

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References

1. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, et al.: Primary prevention of cardiovascular diseases in people with diabetes mellitus: A scientific statement from the American heart association and the American diabetes association. *Diabetes Care* 2007;30:162–172
2. American Diabetes Association Position Statement. Standards of medical care in diabetes-2007. *Diabetes Care* 2007;30(suppl 1):S4–S41
3. Jacobs MJ, Kleisli T, Pio JR, Malik S, L'Italien GJ, et al.: Prevalence and control of dyslipidemia among persons with diabetes in the United States. *Diabetes Res Clin Pract* 2005;70:263–269
4. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, et al.: Implications of recent clinical trials for the National Cholesterol education program adult treatment panel III guidelines. *Circulation* 2004;110:227–239
5. Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, et al.: AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006;113:2363–2372
6. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, et al.: 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;20:614–620
7. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, et al.: Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. *Circulation* 1998;98:2513–2519
8. Keech A, Colquhoun D, Best J, Kirby A, Simes RJ, et al.: Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. *Diabetes Care* 2003;26:2713–2721
9. Collins R, Armitage J, Parish S, Sleigh P, Peto R: MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;361:2005–2016
10. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, et al.: Primary prevention of cardiovascular disease with Atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–696
11. The ALLHAT officers and coordinators for the ALLHAT collaborative research group. Major outcomes in moderately

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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
12. Knopp RH, d'Emden M, Smilde JG, Pocock SJ: Efficacy and safety of Atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 2006;29:1478–1485
13. Sever PS, Poulter NR, Dahlöf B, Wedel H, Collins R, et al.: Reduction in cardiovascular events with Atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial-lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005; 28:1151–1157
14. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, et al.: Intensive lipid lowering with Atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425–1435
15. Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, et al.: Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 2006;29:1220–1226
16. Ahmed S, Cannon CP, Murphy SA, Braunwald E: Acute coronary syndromes and diabetes: is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial. *Eur Heart J* 2006;27: 2323–2329
17. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, et al.: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–1278
18. Costa J, Borges M, David C, Vaz Carneiro A: Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. *BMJ* 2006;332: 1115–1124
19. Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, et al.: Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1999;159:2661–2667
20. Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, et al.: Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 1992;15:820–825
21. Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, 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: 2597–2604
22. Keech A, Simes RJ, Barter P, Best J, Scott R, et al.: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849–1861
23. Karalis D, Ishisaka D, Luo D: Effects of increased dosages of Atorvastatin on the atherogenic lipid subclasses commonly associated with hypertriglyceridemia. *Am J Cardiol* 2007;100: 445–449
24. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, et al.: High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 1989;79: 8–15
25. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, et al.: Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med* 2005;352:29–38
26. van de Ree MA, Huisman MV, Princen HM, Meinders AE, Kluft C: Strong decrease of high sensitivity C-reactive protein with high-dose Atorvastatin in patients with type 2 diabetes mellitus. *Atherosclerosis* 2003;166:129–135
27. Gavish D, Leibovitz E, Shapira I, Rubinstein A: Bezafibrate and simvastatin combination therapy for diabetic dyslipidaemia: efficacy and safety. *J Intern Med* 2000;247:563–569
28. Athyros VG, Papageorgiou AA, Athyrou VV, Demitriadis DS, Kontopoulos AG: Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. *Diabetes Care* 2002;25:1198–1202
29. Davidson MH: Reducing residual risk for patients on statin therapy: the potential role of combination therapy. *Am J Cardiol* 2005;96:3K–13K; discussion 34K–35K
30. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, et al.: Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345: 1583–1592
31. Taylor AJ, Lee HJ, Sullenberger LE: The effect of 24 mo of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr Med Res Opin* 2006;22: 2243–2250
32. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, et al.: Effect of ezetimibe coadministered with Atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation* 2003;107:2409–2415

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