Cost Effectiveness of Statin Therapy for the Primary Prevention of Major Coronary Events in Individuals With Type 2 Diabetes

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OBJECTIVE — To assess the cost and cost effectiveness of hydroxymethylglutaryl (HMG)-CoA reductase inhibitor (statin) therapy for the primary prevention of major coronary events in the U.S. population with diabetes and LDL cholesterol levels ≥100 mg/dl, especially in the population with LDL cholesterol levels 100–129 mg/dl.

RESEARCH DESIGN AND METHODS — Analyses were performed using population estimates from National Health and Nutrition Examination Survey (NHANES)-III, cost estimates from a health system perspective, statin LDL-lowering effectiveness from pivotal clinical trials, and treatment effectiveness from the diabetic subgroup analysis of the Heart Protection Study.

RESULTS — There are ~8.2 million Americans with diabetes, LDL cholesterol levels ≥100 mg/dl, and no clinical evidence of cardiovascular disease. Each year, statin therapy could prevent ~71,000 major coronary events in this population. In the subgroup with LDL cholesterol levels 100–129 mg/dl, the annual cost of statin treatment ranges from $600 to $1,000 per subject. In the population with LDL cholesterol levels ≥130 mg/dl, the annual cost ranges from $700 to $2,100. Annual incremental cost per subject, defined as the cost of statin treatment plus the cost of major coronary events with statin treatment minus the cost of major coronary events without statin treatment, ranges from $480 to $950 in the subgroup with LDL cholesterol levels 100–129 mg/dl and from $590 to $1,920 in the population with LDL cholesterol levels ≥130 mg/dl.

CONCLUSIONS — Statin therapy for the primary prevention of major coronary events in subjects with type 2 diabetes and LDL cholesterol levels 100–129 mg/dl is affordable and cost effective relative to statin therapy in subjects with higher LDL cholesterol levels.

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Abbreviations: 4S, Scandinavian Simvastatin Survival Study; ADA, American Diabetes Association; CABG, coronary artery bypass graft surgery; CHD, coronary heart disease; CVD, cardiovascular disease; HMG, hydroxymethylglutaryl; HPS, Heart Protection Study; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; PTCA, percutaneous transluminal coronary angioplasty; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Cardiovascular disease (CVD) is the major cause of morbidity and mortality in subjects with type 2 diabetes (1,2). Hydroxymethylglutaryl (HMG)-CoA reductase inhibitors (statins) reduce major coronary events and total mortality in diabetic subjects with coronary heart disease (CHD) (3–5). More recently, a primary prevention study (6) suggested and the Heart Protection Study (HPS) demonstrated that in a large subgroup of participants with diabetes and no history of CHD, statin treatment significantly reduces major coronary events (7). The risk of myocardial infarction in diabetic subjects without CHD is as great as in nondiabetic subjects with CHD (8,9). These observations led the American Diabetes Association (ADA) to recommend that in diabetic subjects, hypercholesterolemia be treated as aggressively as in nondiabetic subjects with known CHD (10). The ADA recommends a LDL cholesterol goal <100 mg/dl (2.6 mmol/l) for all patients with diabetes but does not explicitly recommend pharmacological therapy for patients with LDL cholesterol levels between 100 and 129 mg/dl who do not have CVD (10).

The Third National Health and Nutrition Examination Survey (NHANES III) has demonstrated that 29% of Americans with type 2 diabetes and no CVD have LDL cholesterol levels at 100–129 mg/dl and that 56% have LDL cholesterol levels ≥130 mg/dl. The goal of this study was to assess the economic implications of statin therapy for the primary prevention of major coronary events (fatal and nonfatal myocardial infarction [MI] and coronary revascularization) in the U.S. population with diabetes and LDL cholesterol levels at 100–129 mg/dl.

RESEARCH DESIGN AND METHODS

— We analyzed the cost and cost effectiveness of statin treatment for the primary prevention of major coronary events in the U.S. population with

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Table 1—*Effectiveness of lipid-lowering treatment by LDL cholesterol level and statin*

	Lipid-lowering effect (%)	Decrease in LDL (mg/dl)	LDL achieved with treatment (mg/dl)	Cardiac events prevented per year*†
LDL C level 100–129 mg/dl				
Atorvastatin 10 mg	26	26–34	95–74	13,000
Simvastatin 10 mg	27	27–35	94–73	13,500
Lovastatin 20 mg	25	25–32	97–75	12,500
Fluvastatin 40 mg	25	25–32	97–75	12,500
Pravastatin 20 mg	24	24–31	98–76	12,000
LDL C level 130–149 mg/dl				
Atorvastatin 20 mg	39	51–58	91–79	18,500
Simvastatin 20 mg	33	43–49	100–87	15,300
Lovastatin 40 mg	30	39–45	104–91	13,800
Fluvastatin 80 mg	32	42–48	101–88	14,800
Pravastatin 40 mg	29	38–43	106–92	13,200
LDL C level 150–169 mg/dl				
Atorvastatin 20 mg	39	59–66	103–92	21,400
Simvastatin 40 mg	38	57–64	105–93	20,800
Lovastatin 80 mg	36	54–61	108–96	19,500
LDL C level 170–189 mg/dl				
Atorvastatin 40 mg	47	80–89	100–90	9,000
Simvastatin 80 mg	44	75–83	106–95	8,300
LDL C level 190–209 mg/dl				
Atorvastatin 80 mg	47	89–98	111–101	9,500

Data adapted from reference 14. *Cardiac events prevented per year are rounded to nearest 100 and were calculated from the HPS and the UKPDS; †cardiac events per year without statin treatment by baseline LDL cholesterol levels are as follows: 100–129 mg/dl: 44,400; 130–149 mg/dl: 41,700; 150–169 mg/dl: 49,900; 170–189 mg/dl: 17,400; ≥190 mg/dl: 18,800. C, cholesterol.

diabetes using population estimates from NHANES III, cost estimates from the perspective of a large health system, statin LDL-lowering effectiveness from pivotal clinical trials, and the health effects of lowering LDL cholesterol from the HPS (7).

Population estimates

NHANES III was conducted by the National Center for Health Statistics between 1988 and 1994. NHANES III included a nationally representative probability sample of the U.S. civilian noninstitutionalized population, identified through a complex multistage cluster sampling design. We applied weights to account for the unequal probabilities of selection, planned oversampling, and differential nonresponse. Description of the standardized protocols has been published (11). In NHANES III, there were 1,509 subjects with self-reported diabetes and 962 subjects with newly diagnosed diabetes. Of the 2,471 subjects with diabetes, 980 had a proper sampling session and had an assigned weight, and 472 of them had LDL cholesterol measured and no history of MI, angina, or chest pain. The 472 diabetic subjects without a history of MI, angina, or chest pain who were eligible for primary prevention were included in this analysis. The subjects were stratified by 10-mg/dl increments of LDL cholesterol. The distribution of LDL cholesterol levels was then extrapolated to the U.S. population with diagnosed and undiagnosed diabetes and no history of CHD (n = 10,580,000), and the number of diabetic individuals in each stratum was calculated.

Costs

The costs of treatment with statins and of major coronary events were assessed from the perspective of a large health system. The costs of lipid-lowering medication were taken as the 2002 Red Book Average Wholesale Price (AWP). Costs of drug monitoring and adverse experiences were adapted from a cost analysis of the Scandinavian Simvastatin Survival Study (4S) and adjusted to year 2002 U.S. dollars (12). Drug monitoring costs included the cost of lipid profiles and liver function tests and were $51.30 per subject per year. Adverse events with statin treatment are rare (7) and cost $0.40 per subject per year.

The costs of major coronary events were adapted from Grover et al. (13). These included the direct medical costs of fatal and nonfatal MI, coronary artery bypass graft surgery (CABG), and percutaneous transluminal coronary angioplasty (PTCA). In the HPS, 59% of all subjects with a fatal or nonfatal MI underwent coronary revascularization. We assumed that one-half of revascularizations were CABG and one-half were PTCA. The average cost per major coronary event was adjusted to year 2002 U.S. dollars and was $24,445.

Statin effectiveness

The LDL cholesterol–lowering effectiveness of the available statin medications were derived from pivotal clinical trials as summarized in a clinical practice guideline (14). The treatment goal was a LDL cholesterol level ≤100 mg/dl. For each LDL cholesterol stratum, we applied the dosage of available statins that reduced the LDL cholesterol level to target. For example, subjects with LDL cholesterol levels of 100–129 mg/dl could be treated with 10 mg of atorvastatin, 10 mg of simvastatin, 20 mg of lovastatin, 40 mg of fluvastatin, or 20 mg of pravastatin per day to achieve LDL cholesterol levels ≤100 mg/dl (Table 1). Whereas all statins could achieve LDL cholesterol levels <100 mg/dl in subjects with LDL cholesterol levels of 100–129 mg/dl, only one could do so for subjects with LDL cholesterol levels ≥190 mg/dl (Table 1).

Treatment effectiveness

The HPS was a large randomized, placebo-controlled trial of simvastatin in individuals with CHD, other occlusive arterial disease, or diabetes and total cholesterol levels of at least 135 mg/dl (3.5 mmol/l) (7). Of the 20,536 individuals enrolled, 7,150 had no history of CHD and 3,982 of them had diabetes. In the 7,150 without CHD, the mean LDL cholesterol level was 89 mg/dl (2.3 mmol/l) in the treatment group and 128 mg/dl (3.3 mmol/l) in the untreated group. The incidence of major coronary events (nonfatal MI or death from CHD) was 11.0/1,000 person-years in the diabetic subgroup treated with simvastatin and 16.7/1,000 person-years in the diabetic subgroup treated with placebo (15). A 39-mg/dl (1-mmol/l) decrease in LDL cholesterol thus reduced

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Table 2—*Annual costs of statin treatment (medication, monitoring, and adverse events) per patient with diabetes and for the U.S. population with diabetes by baseline LDL cholesterol level*

	LDL 100–129 (mg/dl)	LDL 130–149 (mg/dl)	LDL 150–169 (mg/dl)	LDL 170–189 (mg/dl)	LDL ≥190 (mg/dl)
Population estimates (*n*)	3,023,000	2,243,000	2,300,000	702,000	675,000
Atorvastatin	10 mg	20 mg	**20 mg**	**40 mg**	**80 mg**
Costs per patient/year	$900	$1,300	**$1,300**	**$1,400**	**$1,400**
Total costs in population	$2.66 billion	$2.83 billion	**$2.91 billion**	**$0.95 billion**	**$0.92 billion**
Simvastatin	10 mg	20 mg	40 mg	80 mg	
Costs per patient/year	$1,000	$1,600	$1,600	$1,600	*
Total costs in population	$2.91 billion	$3.67 billion	$3.76 billion	$1.15 billion	*
Lovastatin	20 mg	40 mg	80 mg		
Costs per patient/year	$600	$1,100	$2,100	*	*
Total costs in population	$1.90 billion	$2.46 billion	$4.89 billion	*	*
Fluvastatin	**40 mg**	**80 mg**			
Costs per patient/year	**$600**	**$700**	*	*	*
Total costs in population	**$1.75 billion**	**$1.68 billion**	*	*	*
Pravastatin	20 mg	40 mg			
Costs per patient/year	$1,000	$1,600	*	*	*
Total costs in population	$3.17 billion	$3.62 billion	*	*	*

*Goal of LDL cholesterol–lowering regimen (≤100 mg/dl) cannot be achieved. Bold entries in the table indicate the least expensive statin for each LDL cholesterol stratum.

the incidence of major coronary events by 5.7 events/1,000 person-years (34%) in the diabetic subgroup. In the U.K. Prospective Diabetes Study (UKPDS), LDL cholesterol at baseline was a major risk factor for CHD (16). Fitting the risk factors for CHD as continuous variables indicated that a 39-mg/dl (1-mmol/l) decrease in LDL cholesterol was associated with a 36% reduction in the risk of CHD (16). The incidence of major coronary events per year for statin-treated subjects was calculated using data from the HPS. The incidence of major coronary events for untreated subjects was calculated using data from the HPS (16.7 events per 1,000 person-years for LDL cholesterol 128 mg/dl) and the UKPDS (36% change in risk per each 39-mg/dl change in LDL cholesterol). The difference in incidence of major coronary events between the two groups represents the number of major coronary events per year prevented with statin therapy (Table 1).

Cost effectiveness analysis

Costs were calculated under two hypothetical scenarios, first assuming that all subjects were treated with statins to an LDL cholesterol level <100 mg/dl and then assuming that subjects were treated as they were in the NHANES III and that no additional statin therapy was prescribed. Under the first scenario, costs were calculated as those of statin therapy, drug monitoring, adverse experiences, and major coronary events. Under the second scenario, costs were calculated as the costs of major coronary events only. The difference in costs between the treatment and nontreatment scenarios (incremental cost) was described both on a per patient basis and for the U.S. population with diabetes and no history of CHD.

Sensitivity analyses

Sensitivity analyses were performed to assess the impact of plausible changes in underlying assumption on the results. The base-case analysis was performed with the least-expensive statin for each LDL cholesterol stratum. Sensitivity analyses were performed by increasing or decreasing the cost of statins or major coronary events by 25% or the incidence of major coronary events with or without statin treatment by 25%. Increasing or decreasing the cost of major coronary events by 25% changed the cost from approximately $24,400 to $30,600 or $18,300. If all subjects requiring revascularization underwent CABG and none PTCA, the cost of a major coronary event would be $30,400, similar to the upper bound of the sensitivity analysis. Likewise, if all subjects underwent PTCA and none CABG the cost of a major coronary event would be $18,500, similar to the lower bound. All analyses were performed using Excel spreadsheets and DATA 3.0 decision analysis software (TreeAge Software, Williamstown, MA).

RESULTS

— Based on data from the NHANES III, we estimated that ~1.6 million Americans with diabetes and without CHD have LDL cholesterol levels <100 mg/dl, 3.0 million have levels of 100–129 mg/dl, 2.2 million have levels of 130–149 mg/dl, 2.3 million have levels of 150–169 mg/dl, 700,000 have levels of 170–189 mg/dl, and 700,000 have LDL cholesterol levels ≥190 mg/dl.

Based on treatment effectiveness data, we assigned various statins and dosages to achieve LDL cholesterol levels <100 mg/dl (Table 1). The annual per capita costs of statin therapy (including medication, drug monitoring, and adverse experiences) and total costs of statin therapy for each LDL cholesterol stratum are shown in Table 2. Treatment of LDL cholesterol levels between 100 and 129 mg/dl to achieve LDL cholesterol levels <100 mg/dl cost $600 to $1,000 per patient per year depending on the statin prescribed. Annual per capita costs of statin therapy ranged from $700 to $2,100 in the groups with LDL cholesterol levels ≥130 mg/dl. If subjects with LDL cholesterol levels between 100 and 129 mg/dl are treated with

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Table 3—*Annual incremental costs of statin treatment* per patient with diabetes and for the U.S. population with diabetes by baseline LDL cholesterol levels*

	LDL 100–129 (mg/dl)	LDL 130–149 (mg/dl)	LDL 150–169 (mg/dl)	LDL 170–189 (mg/dl)	LDL ≥190 (mg/dl)
Population estimates (*n*)	3,023,000	2,243,000	2,300,000	702,000	675,000
Atorvastatin					
Net costs per subject	$780	$1,060	**$1,040**	**$1,050**	**$1,020**
Net costs for population	$2.34 billion	$2.38 billion	**$2.38 billion**	**$0.74 billion**	**$0.69 billion**
Simvastatin					
Net costs per subject	$850	$1,470	$1,410	$1,350	†
Net costs for population	$2.58 billion	$3.29 billion	$3.25 billion	$0.94 billion	†
Lovastatin					
Net costs per subject	$530	$950	$1,920	†	†
Net costs for population	$1.59 billion	$2.12 billion	$4.41 billion	†	†
Fluvastatin					
Net costs per subject	**$480**	**$590**	†	†	†
Net costs for population	**$1.45 billion**	**$1.32 billion**	†	†	†
Pravastatin					
Net costs per subject	$950	$1,470	†	†	†
Net costs for population	$2.87 billion	$3.29 billion	†	†	†

*Incremental costs = costs of statin treatment (medication, monitoring, and adverse events) plus costs of major coronary events with statin treatment minus cost of major coronary events without statin treatment; †Goal of LDL cholesterol–lowering regimen (≤100 mg/dl) cannot be achieved. Bold entries in the table indicate the least expensive statin for each LDL cholesterol stratum.

the least expensive statin, total annual costs are $1.8 billion. Treatment of all subjects with LDL cholesterol levels ≥130 mg/dl costs $6.5 to $10.6 billion.

With treatment effectiveness data from the HPS and UKPDS, we estimated that ~101,000 major coronary events per year would occur if the population was treated with statins and ~172,000 events would occur if the population was not treated with statins. Statin treatment would thus prevent ~71,000 major coronary events per year in the U.S. population with diabetes and no CHD, 18% (13,000) of these in the population with LDL cholesterol levels of 100–129 mg/dl.

The incremental cost of statin treatment may be defined as the cost of statin therapy (medication, monitoring, and adverse events) plus the cost of major coronary events if the population is treated with statins minus the cost of major coronary events if the population is not treated with statins. Each major coronary event costs ~$24,400. In the subgroup with LDL cholesterol levels between 100 and 129 mg/dl, major coronary events would cost approximately $0.77 billion per year if the subgroup was treated with statins and $1.09 billion per year if the subgroup was not treated with statins. In the population with LDL cholesterol levels ≥130 mg/dl, major coronary events would cost approximately $1.70 billion per year if subjects were treated with statins and $3.13 billion per year if subjects were not treated with statins. The incremental costs per subject and for the population are shown in Table 3. The incremental cost per subject ranged from $480 to $950 per year in the subgroup with LDL cholesterol levels between 100 and 129 mg/dl and from $590 to $1,920 per year in the population with LDL cholesterol levels ≥130 mg/dl. The incremental cost of statin treatment per subject generally increased with higher baseline LDL cholesterol levels. If the least expensive statin was prescribed for each LDL cholesterol stratum, the incremental cost of statin treatment per subject would range from $480 to $1,050 per year depending on the baseline LDL cholesterol level.

Sensitivity analysis

Sensitivity analyses are shown in Table 4. If the cost of major coronary events, the incidence of major coronary events without statin treatment, or the incidence of major coronary events with statin treatment increased or decreased by 25%, the incremental costs would change only modestly. The incremental costs of treatment are most sensitive to changes in the cost of statin therapy. If the cost of statin therapy was 25% higher than in the base-case analysis, the incremental cost would increase by one-third and range from $620 to $1,390 per subject with diabetes. Similarly, if the cost of statin treatment was 25% lower, the incremental cost would decrease by about one-third and range from $330 to $720 per subject with diabetes.

CONCLUSIONS — For diabetic subjects without CHD, the ADA recommends starting pharmacological therapy for LDL cholesterol levels ≥130 mg/dl with the treatment goal at <100 mg/dl (10). In subjects with LDL cholesterol levels between 100 and 129 mg/dl, a variety of treatment strategies have been recommended, including aggressive medical nutrition therapy and statin therapy (10). About 3.0 million subjects or 29% of the U.S. population with diabetes and without CHD have LDL cholesterol levels between 100 and 129 mg/dl. Prescribing statin therapy for this group would cost between $1.8 and $3.2 billion for the U.S. health system. The cost of treating such subjects with the least expensive statin ($1.8 billion) is less than half the difference in the costs of treating subjects with LDL cholesterol levels ≥130 mg/dl with the most expensive statin versus the least expensive statin ($4.1 billion). The incremental cost of statin treatment is generally lower in the diabetic subgroup with LDL cholesterol levels at 100–129 mg/dl than

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Table 4—*Sensitivity analysis of incremental cost of statin treatment per patient with diabetes by baseline LDL cholesterol level**

	LDL 100–129 (mg/dl)	LDL 130–149 (mg/dl)	LDL 150–169 (mg/dl)	LDL 170–189 (mg/dl)	LDL ≥190 (mg/dl)
Base-case analysis	**$480**	**$590**	**$1,040**	**$1,050**	**$1,020**
Cost of statin					
Increase by 25%	$620	$770	$1,350	$1,390	$1,360
Decrease by 25%	$330	$400	$720	$710	$680
Cost of coronary event					
Increase by 25%	$450	$550	$980	$970	$930
Decrease by 25%	$500	$630	$1,090	$1,130	$1,100
Incidence of coronary events with statin treatment					
Increase by 25%	$540	$660	$1,110	$1,120	$1,100
Decrease by 25%	$410	$510	$960	$970	$930
Incidence of coronary events without statin treatment					
Increase by 25%	$390	$470	$900	$900	$840
Decrease by 25%	$570	$700	$1,170	$1,200	$1,190

*Base-case analysis was performed with the least-expensive statin for each LDL cholesterol stratum.

in those with LDL cholesterol levels ≥130 mg/dl due to lower medication costs. Sensitivity analyses indicate that the incremental costs of statin treatment are most sensitive to changes in the cost of statin therapy. Thus, the use of the least expensive effective statin within each LDL cholesterol stratum, including the use of generic statins, would decrease the incremental cost substantially.

The recommendation for aggressive LDL cholesterol–lowering in the diabetic population with LDL cholesterol levels of 100–129 mg/dl is supported by findings in observational studies and large randomized controlled clinical trials (7,16). The observational findings of the UKPDS indicate that a 39-mg/dl (1-mmol/l) decrease in LDL cholesterol is associated with a 36% reduction in the risk of CHD (16). The HPS demonstrated that in diabetic subjects with no preexisting CHD, statin therapy that lowered LDL cholesterol by 39 mg/dl (1 mmol/l) reduced major vascular events (major coronary events, strokes of any type, and coronary and noncoronary revascularizations) by 25% and major coronary events by 34% (7,15). More importantly, the study demonstrated that lowering LDL cholesterol from <3 mmol/l (116 mg/dl) to <2 mmol/l (77 mg/dl) reduced the risk of major vascular events by one-quarter.

Economic analyses of statin therapy have been performed for diabetic subjects with and without CHD. A post hoc subgroup analysis from the 4S that examined lipid-lowering treatment in 202 diabetic subjects with CHD revealed that simvastatin reduced CVD-related hospitalizations and total hospital days and generated net savings of $1,801 (1998 U.S. dollars) in direct medical cost per subject (12). Grover et al. (13) used a Markov model to compare the long-term costs and benefits of treating dyslipidemia in diabetic patients without CVD. Treatment with simvastatin among diabetic subjects without CVD cost between $5,063 and $23,792 (1998 U.S. dollars) per year of life saved (13). The study by Grover et al. differs from our study in several ways. First, we estimated treatment effectiveness from a primary prevention study, whereas they extrapolated treatment effectiveness from a secondary intervention study. Second, the target LDL cholesterol level in our study was 100 mg/dl or less compared with 122 mg/dl in their study.

Some limitations of our study deserve mention. First, the sample of diabetic subjects in NHANES III with measured LDL cholesterol levels and no CHD was relatively small. Nevertheless, the estimates from NHANES III were weighted to represent the U.S. population and are the best data available. Second, our analyses were limited by the limitations of reports published in the literature. LDL cholesterol levels at baseline and with treatment were not reported in the HPS for the diabetic subpopulation without CHD. Because LDL cholesterol levels in the diabetic population do not differ greatly from those in the general population, we assumed that they were the same as for the total population without CHD. Third, our study may have overestimated the benefits of statin therapy because we applied results from randomized controlled clinical trials to the general population with diabetes. Because compliance with therapy is higher in clinical trials, the benefit of statin therapy may be less in the general population with diabetes. Fourth, our study may have underestimated the benefit of statin therapy in subjects with diabetes because we did not assess the beneficial effects of statin treatment on the incidence of stroke and peripheral vascular disease. The HPS demonstrated that statin therapy prevented not only coronary events and revascularization, but also ischemic strokes and peripheral revascularizations (7). Finally, we did not account for the treatment of other cardiovascular risk factors when assessing the incidence of major coronary events. To the extent that control of other cardiovascular risk factors is better or worse in the general diabetic population than it was in the HPS and UKPDS populations, we may have overestimated or underestimated the benefit of statin therapy.

In conclusion, from a health system perspective, statin therapy for the primary prevention of major coronary events in subjects with type 2 diabetes and LDL cholesterol levels of 100–129 mg/dl is affordable and cost effective relative to sta-

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tin therapy for diabetic subjects with higher LDL cholesterol levels. However, statin therapy for primary prevention of major coronary events in subjects with type 2 diabetes is not cost saving regardless of the baseline LDL cholesterol level.

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