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Cost-Effectiveness of Cholesterol-Lowering Therapies according to Selected Patient Characteristics

Lisa A. Prosser, MS; Aaron A. Stinnett, PhD; Paula A. Goldman, MPH; Lawrence W. Williams, MSc; Maria G.M. Hunink, MD, PhD; Lee Goldman, MD, MPH; and Milton C. Weinstein, PhD

Background: The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II) recommends treatment guidelines based on cholesterol level and number of risk factors.

Objective: To evaluate how the cost-effectiveness ratios of cholesterol-lowering therapies vary according to different risk factors.

Design: Cost-effectiveness analysis.

Data Sources: Published data.

Target Population: Women and men 35 to 84 years of age with low-density lipoprotein cholesterol levels of 4.1 mmol/L or greater (≥160 mg/dL), divided into 240 risk subgroups according to age, sex, and the presence or absence of four coronary heart disease risk factors (smoking status, blood pressure, low-density lipoprotein cholesterol level, and high-density lipoprotein cholesterol level).

Time Horizon: 30 years.

Perspective: Societal.

Interventions: Step I diet, statin therapy, and no preventive treatment for primary and secondary prevention.

Outcome Measures: Incremental cost-effectiveness ratios.

Results of Base-Case Analysis: Incremental cost-effectiveness ratios for primary prevention with step I diet ranged from $1900 per quality-adjusted life-year (QALY) gained to $500 000 per QALY depending on risk subgroup characteristics. Primary prevention with a statin compared with diet therapy was $54 000 per QALY to $1 400 000 per QALY. Secondary prevention with a statin cost less than $50 000 per QALY for all risk subgroups.

Results of Sensitivity Analysis: The inclusion of niacin as a primary prevention option resulted in much less favorable incremental cost-effectiveness ratios for primary prevention with a statin (>$500 000 per QALY).

Conclusions: Cost-effectiveness of treatment strategies varies significantly when adjusted for age, sex, and the presence or absence of additional risk factors. Primary prevention with a step I diet seems to be cost-effective for most risk subgroups but may not be cost-effective for otherwise healthy young women. Primary prevention with a statin may not be cost-effective for younger men and women with few risk factors, given the option of secondary prevention and of primary prevention in older age ranges. Secondary prevention with a statin seems to be cost-effective for all risk subgroups and is cost-saving in some high-risk subgroups.

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For author affiliations, current addresses, and contributions, see end of text.

Several large-scale, long-term clinical trials evaluating statin drugs (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have confirmed the beneficial effect of reducing cholesterol levels on coronary event rates and related mortality (1–5). Statin drugs are expensive, especially considering the large number of persons who could potentially benefit from cholesterol-lowering therapies. As a result, many analyses have focused on the costs, resource use, and cost-effectiveness of using statins to lower cholesterol levels (6–15).

In this analysis, the cost-effectiveness of primary and secondary prevention with cholesterol-lowering therapies was evaluated in separate risk subgroups to assess how cost-effectiveness varies with individual patient characteristics. This analysis extends the results of previous analyses by examining a greater number of specific patient subgroups, particularly with respect to primary prevention. It improves on previous analyses by including updated costs and epidemiologic estimates and by following recommendations from the U.S. Panel on Cost-Effectiveness in Health and Medicine. The incremental cost-effectiveness of statins compared with diet therapy

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was explicitly modeled. Finally, we compared the cost-effectiveness results with the treatment guidelines recommended by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II) (16).

Methods

The analysis used a previously validated computer simulation model, the Coronary Heart Disease Policy Model (17–19), to estimate the effects and costs of each cholesterol-lowering strategy in each risk group. The assumptions and design of the Coronary Heart Disease Policy Model are described in detail elsewhere (17, 18). The model consists of three integrated submodels: the demographic-epidemiologic submodel, the bridge submodel, and the disease history submodel.

The demographic-epidemiologic submodel predicts coronary heart disease incidence and non–coronary heart disease mortality among people 35 to 84 years of age without coronary heart disease. The risk function for incidence of coronary heart disease is based on age, sex, diastolic blood pressure, smoking status, low-density lipoprotein (LDL) cholesterol level, and high-density lipoprotein (HDL) cholesterol level. The risk function for non–coronary heart disease mortality includes age, sex, diastolic blood pressure, and smoking status. Non–coronary heart disease mortality is assumed to be unaffected by serum cholesterol levels (1, 2).

After a person in the model develops coronary heart disease, he or she moves into the bridge submodel, which characterizes the initial coronary heart disease event (cardiac arrest, myocardial infarction, or angina) and the sequelae in the first 30 days after the event. The disease history submodel tracks the subsequent development of coronary heart disease events, revascularization procedures (coronary artery bypass grafting and angioplasty), coronary heart disease mortality, and non–coronary heart disease mortality among patients with coronary heart disease.

Target Population

The base-case analysis evaluated the cost-effectiveness of primary and secondary prevention in all persons with LDL cholesterol levels of 4.1 mmol/L or greater (≥160 mg/dL). Specific subgroup analyses examined how the cost-effectiveness changed according to patient age (35 to 44, 45 to 54, 55 to 64, 65 to 74, or 75 to 84 years), sex, smoking status (yes or no), diastolic blood pressure (<95 mm Hg or ≥95 mm Hg), HDL cholesterol level (<0.9, 0.9 to 1.3, or >1.3 mmol/L [<35, 35 to 49, or ≥50 mg/dL]), and LDL cholesterol level (4.2 to 4.9 or ≥4.9 mmol/L [160 to 189 or ≥190 mg/dL]). These risk factors closely correspond to but are not exactly the same as the National Cholesterol Education Program risk factor definitions (16).

Effectiveness

Lipid Levels

Results from five studies were pooled to estimate the effects of a low-cholesterol diet (step I diet) on cholesterol levels (20–24). Data used to model the effectiveness of primary prevention with a statin came from three long-term studies of pravastatin, 40 mg/d, because the quality of effectiveness data was high for this dosage (2, 25, 26). Effectiveness estimates for secondary prevention with a statin was based on results from the Scandinavian Simvastatin Survival Study (**Appendix Table**) (1).

A 2-year time lag between the start of treatment and the effects of treatment on coronary events was assumed (1, 2).

Quality of Life

Quality-of-life weights in the general population without coronary heart disease were based on data from the Beaver Dam Health Outcomes Study according to age and sex (27). Additional quality-of-life adjustments for coronary heart disease–related morbidity were made for persons in the disease history submodel; because community preferences were not available, these adjustments were based on a survey of Medicare patients with a history of coronary heart disease (28, 29).

Costs

In the Coronary Heart Disease Policy Model, total costs were calculated as the sum of intervention costs, costs of coronary heart disease care, and costs of non–coronary heart disease health care. All costs were converted to 1997 U.S. dollars by using the Medical Care Component of the Consumer Price Index.

Intervention costs included the costs of medication, physician visits (including the associated patient time), and laboratory tests. National Cholesterol Education Program guidelines were used to guide estimates of the number of physician visits and laboratory tests each year (16).

Medication

Medication costs for primary and secondary prevention with statins were calculated by using the average wholesale prices of pravastatin and simvastatin, respectively (30). The base-case analysis does not include adjustment of future medication costs resulting from loss of patent protection for statin drugs. To adjust for compliance, it was assumed that patients receiving statins take 95% of the suggested regimen (31); this average compliance rate is reflected in the pool of studies from which the estimates of effectiveness were derived (**Appendix Table**).

Primary Prevention

Patients receiving diet therapy were assumed to have two physician visits per year. Patients receiving primary prevention with a statin were assumed to have five physician visits in the first year and two physician visits in each year after the first year. A cost of $34.34 was associated with each office visit (32, 33). In addition, the value of patient time associated with each visit was estimated by multiplying the average time per visit (including travel, waiting, and encounter times) by age- and sex-specific average hourly wages. These age- and sex-adjusted patient time costs range from approximately $12 to $26 per physician visit (34, 35).

Patients receiving diet therapy were assumed to have one chemical profile, one HDL measurement, and one mid-year measurement of total cholesterol, for a total annual laboratory cost of $39.49 (36). Patients receiving drug therapy were assumed to receive five sets of tests in the first year (five chemical profiles and five HDL measurements for a cost of $151.55) and two sets of tests in each subsequent year ($60.62) (36).

The resulting cost estimate of primary prevention with step I diet was $108 per year. For primary prevention with a statin, cost estimates were $1512 in the first year and $1318 in subsequent years. Annual age- and sex-specific patient time costs of $25 to $59 were added to these estimates.

Secondary Prevention

For secondary prevention, it was assumed that patients would already be seeing their physicians for reasons related to their previous coronary heart disease event. Patient time costs, additional laboratory costs of measuring cholesterol, and costs of cholesterol-lowering medication were the only additional intervention-related costs associated with secondary prevention. The annual cost of secondary prevention with a statin was estimated to be $1329 (excluding patient time costs).

Coronary Heart Disease

Costs of treating coronary heart disease are also included in the model and are described in detail elsewhere (8). These include the costs of hospitalization; physician visits; laboratory tests; pharmaceuticals associated with a coronary heart disease event; and any associated procedures, such as coronary artery bypass grafting, coronary angioplasty, and cardiac catheterization.

Non–Coronary Heart Disease Health Care

The analysis included annual costs related to non–coronary heart disease health care that were developed from the 1987 National Medical Expenditure Survey. Details of the calculation are described elsewhere (8).

Cost-Effectiveness Analysis

An incremental cost-effectiveness ratio is the difference in time-discounted costs between the evaluated strategy and the comparison strategy divided by the difference in time-discounted quality-adjusted life-years (QALYs) between the two strategies. For each incremental cost-effectiveness comparison, we examined the cost-effectiveness of extending therapy to a new indication, assuming that the decision had been made to use it in situations with more favorable cost-effectiveness ratios. For example, for primary prevention, statin therapy was compared with step I diet, and step I diet was compared with no primary prevention. For the age-specific analyses, we assumed that once treatment was initiated at a given age, it would be continued through older age ranges, in which treatment typically had more favorable cost-effectiveness results. All analyses of primary prevention assumed a backdrop of secondary prevention with a statin. A separate analysis of the cost-effectiveness of secondary prevention with a statin compared with no secondary prevention was also performed within each risk factor group.

Additional Assumptions

A discontinuation rate of 6% because of adverse affects was assumed for both primary and secondary prevention with statins (1, 2, 26, 37–39).

The analysis was conducted from the societal perspective. Effects and costs were evaluated over a 30-year time frame. Costs and quality-adjusted life-years were discounted at an annual rate of 3%. Cost-effectiveness ratios were reported to two significant digits, as recommended by the Cost-Effectiveness Panel (40), reflecting the precision of the input data. This analysis adhered to the recommendations of the U.S. Panel on Cost-Effectiveness in Health and Medicine for conducting a reference-case cost-effectiveness analysis (40).

Sensitivity Analysis

Sensitivity analyses were performed on cost of diet and statin therapy, health-related quality-of-life weights, effectiveness of step I diet, lag time between initiation of treatment and its effect on coronary heart disease event rates, logistic regression coefficients for the effects of LDL and HDL cholesterol levels on coronary heart disease event rates in the model, and the inclusion of niacin as a treatment option for primary prevention.

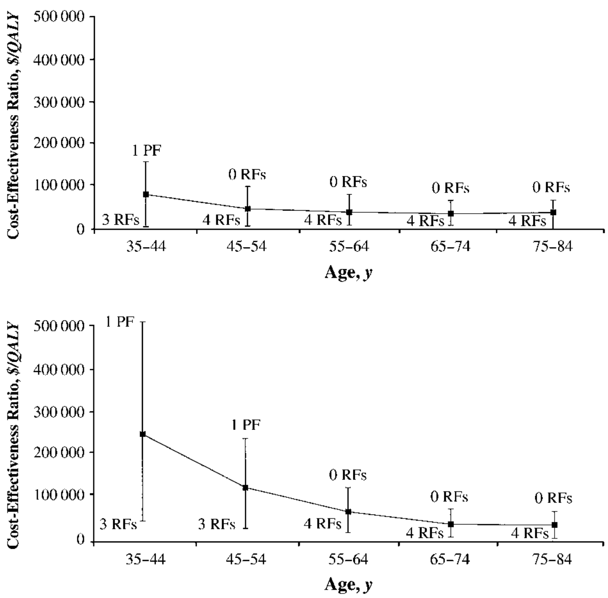

Figure 1. Cost-effectiveness of primary prevention with diet in men (*top*) and women (*bottom*) with low-density lipoprotein cholesterol levels of 4.1 mmol/L or greater (≥160 mg/dL). Squares represent results of the base-case analysis for cost-effectiveness by age and sex without considering additional risk factors. Bars represent the range of cost-effectiveness by age group once selected additional risk factors are considered. The number of risk factors per subgroup ranged from no risk factors (*RFs*) or one protective factor (*PF*) to three or four risk factors per subgroup. QALY = quality-adjusted life-year.

For the sensitivity analysis that included niacin as a treatment option for primary prevention, the effect of treatment was modeled by using results pooled from three studies with an average immediate-release niacin dosage of 1.3 g/d (41–43). The total annual cost of primary prevention with niacin was estimated to be $361 in the first year and $163 in subsequent years (excluding patient time costs). This includes the costs for one daily 325-mg tablet of aspirin in the first year to alleviate the side effect of flushing (44). Patients taking niacin are assumed to have a discontinuation rate of 27.3% (45) and on average take 90% of the suggested dose (46).

Role of the Funding Source

The study was supported by the Agency for Healthcare Research and Quality and a training grant from the National Library of Medicine. The study sponsors played no role in the design, conduct, or reporting of the trial.

Results

Cost-effectiveness ratios for step I diet therapy were generally less than $100 000 per QALY for men and women with more than one risk factor (except for some women <45 years of age). Cost-effectiveness ratios for primary prevention with a statin varied widely according to risk factor subgroup, from $54 000 per QALY to $420 000 per QALY for men and from $62 000 per QALY to $1 400 000 per QALY for women, and were greater than $100 000 per QALY for many risk subgroups.

Table 1. Cost-Effectiveness of Primary Prevention with Diet in Men*

Low-Density Lipoprotein Cholesterol Level	Diastolic Blood Pressure	Smoking Status	High-Density Lipoprotein Cholesterol Level	Risk Factors†‡	Cost-Effectiveness				
					Age 35–44 y	Age 45–54 y‡	Age 55–64 y‡	Age 65–74 y‡	Age 75–84 y‡
mmol/L (mg/dL)	*mm Hg*		*mmol/L (mg/dL)*	*n*	←— *$/QALY* —→				
4.2–4.9 (160–189)	<95	Nonsmoker	>1.3 (49)	−1	160 000	100 000	82 000	68 000	70 000
	<95	Smoker	>1.3 (49)	0	130 000	100 000	88 000	66 000	1900
	<95	Nonsmoker	0.9–1.3 (35–49)	0	130 000	73 000	54 000	46 000	47 000
	≥95	Nonsmoker	>1.3 (49)	0	71 000	74 000	55 000	40 000	2400
	<95	Nonsmoker	<0.9 (35)	1	79 000	44 000	40 000	36 000	28 000
	≥95	Nonsmoker	0.9–1.3 (35–49)	1	60 000	50 000	36 000	28 000	15 000
	≥95	Smoker	>1.3 (49)	1	65 000	72 000	58 000	39 000	1900
	<95	Smoker	0.9–1.3 (35–49)	1	100 000	63 000	51 000	42 000	14 000
	≥95	Nonsmoker	<0.9 (35)	2	30 000	30 000	27 000	23 000	1900
	<95	Smoker	<0.9 (35)	2	50 000	36 000	37 000	32 000	1900
	≥95	Smoker	0.9–1.3 (35–49)	2	44 000	43 000	33 000	25 000	1900
	≥95	Smoker	<0.9 (35)	3	22 000	23 000	24 000	21 000	1900
>4.9 (≥190)	<95	Nonsmoker	>1.3 (49)	−1	100 000	54 000	44 000	38 000	34 000
	<95	Nonsmoker	0.9–1.3 (35–49)	0	65 000	32 000	26 000	27 000	27 000
	≥95	Nonsmoker	>1.3 (49)	0	46 000	37 000	27 000	21 000	1900
	<95	Smoker	>1.3 (49)	0	96 000	53 000	45 000	38 000	1900
	<95	Smoker	0.9–1.3 (35–49)	1	59 000	29 000	25 000	24 000	1900
	≥95	Smoker	>1.3 (49)	1	44 000	35 000	28 000	21 000	1900
	≥95	Nonsmoker	0.9–1.3 (35–49)	1	29 000	21 000	16 000	15 000	1900
	<95	Nonsmoker	<0.9 (35)	1	31 000	18 000	18 000	20 000	14 000
	≥95	Nonsmoker	<0.9 (35)	2	9800	10 000	11 000	12 000	1900
	<95	Smoker	<0.9 (35)	2	22 000	15 000	17 000	18 000	1900
	≥95	Smoker	0.9–1.3 (35–49)	2	22 000	17 000	14 000	14 000	1900
	≥95	Smoker	<0.9 (35)	3	6700	7800	9500	10 000	1900

* QALY = quality-adjusted life-year.
† Not including age.
‡ Add one risk factor for men 45 years of age or older.

Table 2. Cost-Effectiveness of Primary Prevention with Diet in Women*

Low-Density Lipoprotein Cholesterol Level	Diastolic Blood Pressure	Smoking Status	High-Density Lipoprotein Cholesterol Level	Risk Factors†‡	Cost-Effectiveness				
					Age 35–44 y	Age 45–54 y	Age 55–64 y‡	Age 65–74 y‡	Age 75–84 y‡
mmol/L (mg/dL)	*mm Hg*		*mmol/L (mg/dL)*	*n*	← $/QALY →				
4.2–4.9 (160–189)	<95	Nonsmoker	>1.3 (49)	−1	490 000	230 000	120 000	73 000	68 000
	<95	Smoker	>1.3 (49)	0	500 000	250 000	150 000	87 000	55 000
	<95	Nonsmoker	0.9–1.3 (35–49)	0	320 000	120 000	64 000	43 000	41 000
	≥95	Nonsmoker	>1.3 (49)	0	240 000	140 000	69 000	44 000	38 000
	<95	Nonsmoker	<0.9 (35)	1	210 000	81 000	52 000	31 000	24 000
	≥95	Nonsmoker	0.9–1.3 (35–49)	1	150 000	76 000	36 000	26 000	22 000
	≥95	Smoker	>1.3 (49)	1	220 000	150 000	85 000	50 000	8200
	<95	Smoker	0.9–1.3 (35–49)	1	310 000	120 000	78 000	49 000	22 000
	≥95	Nonsmoker	<0.9 (35)	2	74 000	43 000	25 000	17 000	8200
	<95	Smoker	<0.9 (35)	2	210 000	91 000	64 000	37 000	8200
	≥95	Smoker	0.9–1.3 (35–49)	2	110 000	73 000	42 000	27 000	8200
	≥95	Smoker	<0.9 (35)	3	58 000	47 000	31 000	20 000	8200
>4.9 (≥190)	<95	Nonsmoker	>1.3 (49)	−1	180 000	130 000	71 000	37 000	36 000
	<95	Nonsmoker	0.9–1.3 (35–49)	0	110 000	63 000	34 000	21 000	22 000
	≥95	Nonsmoker	>1.3 (49)	0	150 000	86 000	44 000	26 000	17 000
	<95	Smoker	>1.3 (49)	0	170 000	140 000	94 000	48 000	19 000
	<95	Smoker	0.9–1.3 (35–49)	1	120 000	72 000	45 000	25 000	8200
	≥95	Smoker	>1.3 (49)	1	130 000	87 000	53 000	30 000	8200
	≥95	Nonsmoker	0.9–1.3 (35–49)	1	94 000	42 000	21 000	15 000	10 000
	<95	Nonsmoker	<0.9 (35)	1	100 000	48 000	31 000	18 000	9500
	≥95	Nonsmoker	<0.9 (35)	2	43 000	25 000	16 000	11 000	8200
	<95	Smoker	<0.9 (35)	2	110 000	57 000	39 000	22 000	8200
	≥95	Smoker	0.9–1.3 (35–49)	2	88 000	43 000	25 000	15 000	8200
	≥95	Smoker	<0.9 (35)	3	46 000	29 000	20 000	11 000	8200

* QALY = quality-adjusted life-year.
† Not including age.
‡ Add one risk factor for women 55 years of age or older.

Cost-effectiveness ratios for secondary prevention with a statin were less than $50 000 per QALY for all risk subgroups.

Primary Prevention with Step I Diet

For step I diet therapy compared with no primary prevention for persons with LDL cholesterol levels of 4.1 mmol/L or greater (≥160 mg/dL), cost-effectiveness ratios in the base-case analysis ranged from $37 000 per QALY for men 65 to 74 years of age to $82 000 for men 35 to 44 years of age (**Figure 1**). Cost-effectiveness ratios in the base-case analysis ranged from $38 000 per QALY for women 75 to 84 years of age to $236 000 per QALY for women 35 to 44 years of age (**Figure 1**). When individual risk factors were considered, cost-effectiveness ratios ranged from $1900 per QALY for men 75 to 84 years of age with four risk factors to $500 000 per QALY for women 35 to 44 years of age with no risk factors. Cost-effectiveness ratios depend on the specific risk factor combination, not just the total number of risk factors (**Tables 1** and **2**).

Primary Prevention with a Statin

For men with an LDL cholesterol level of 4.1 mmol/L or greater (≥160 mg/dL), the cost-effectiveness of primary prevention with a statin compared with primary prevention with step I diet ranged from $130 000 per QALY to $260 000 per QALY (**Figure 2**). When individual risk factors were considered, the range of cost-effectiveness for this treatment strategy expanded to $54 000 to $420 000 per QALY (**Table 3**).

For women with an LDL cholesterol level of 4.1 mmol/L or greater (≥160 mg/dL), the variation in cost-effectiveness ratios when risk factors were included was even more noteworthy. Cost-effectiveness ratios for the base-case analysis started at $150 000 per QALY for women 65 to 74 years of age and increased to $730 000 per QALY for women 35 to 44 years of age (**Figure 2**). When individual risk factors were considered, the cost-effectiveness for primary prevention with a statin in women ranged from $62 000 per QALY to $1 400 000 per QALY (**Table 4**).

In general, cost-effectiveness ratios became more favorable with increasing numbers of risk factors, although certain risk factors, such as diastolic blood pressure and HDL cholesterol level, had a greater impact on cost-effectiveness than did others. Cost-effectiveness ratios also became more favorable as age increased. Cost-effectiveness ratios for women were higher than those for men.

Secondary Prevention with a Statin

Detailed results for the cost-effectiveness of secondary prevention were analyzed and were similar to those of other studies (10, 11, 13). Cost-effectiveness ratios were less than $50 000 per QALY for all risk subgroups and were approximately $10 000 per

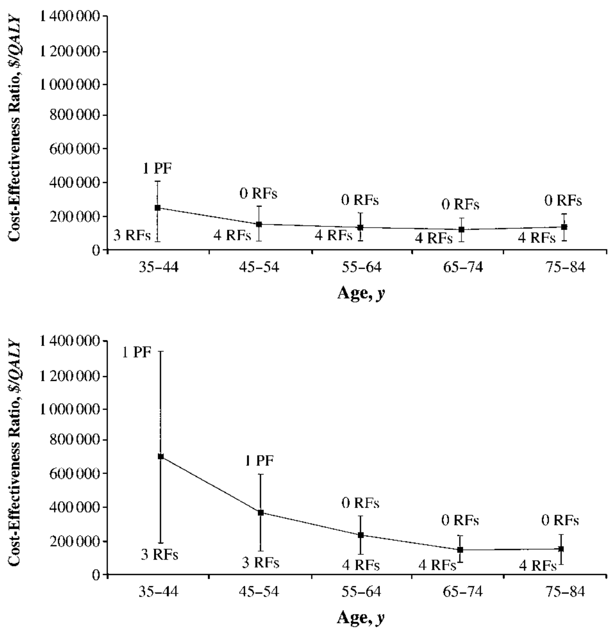

Figure 2. Cost-effectiveness of primary prevention with pravastatin in men (*top*) and women (*bottom*) with low-density lipoprotein cholesterol levels of 4.1 mmol/L or greater (≥160 mg/dL). Squares represent results of the base-case analysis for cost-effectiveness by age and sex without considering additional risk factors. Bars represent range of cost-effectiveness by age group once selected additional risk factors are considered. The number of risk factors per subgroup ranged from no risk factors (*RFs*) or one protective factor (*PF*) to three or four risk factors per subgroup. QALY = quality-adjusted life-year.

QALY or less for most risk subgroups. Secondary prevention with a statin was cost saving for many subgroups of men with one or more risk factors (**Table 5**).

Sensitivity Analysis

Because drug costs represent approximately 90% of the costs associated with primary prevention with a statin, sensitivity analysis assuming a 50% decrease in drug costs resulted in an almost proportionate decrease in cost-effectiveness ratios (ranging from 44% to 55% of the original cost-effectiveness ratios). Given that cost-effectiveness ratios are almost directly proportional to drug costs, one can roughly estimate the effect of a change in drug costs. For example, statin treatment in men 65 to 74 years of age with an LDL cholesterol level of 4.2 to 4.9 mmol/L (160 to 189 mg/dL) and two risk factors (smoking and age > 45 years) will become cost-effective at a threshold of $50 000 per QALY at approximately one third of the cost used in the base-case analysis.

When a lag time of less than 2 years was modeled, cost-effectiveness ratios for primary prevention with statin or diet therapy became more favorable for older age groups and less favorable for younger age groups. The result in younger age groups occurs because the alternative strategy of delaying treatment is now more beneficial (no lag) without being more costly. For men 55 years of age or older, cost-effectiveness ratios would decrease by 10% to 50% if there were no time lag in benefits. Cost-effectiveness ratios remained similar for men 45 to 54 years of age but doubled for men 35 to 44 years of age. Cost-effectiveness ratios decreased by 40% to 50% for women 75 to 84 years of age, remained

Table 3. Cost-Effectiveness of Primary Prevention with a Statin in Men*

Low-Density Lipoprotein Cholesterol Level	Diastolic Blood Pressure	Smoking Status	High-Density Lipoprotein Cholesterol Level	Risk Factors†‡	Cost-Effectiveness				
					Age 35–44 y	Age 45–54 y‡	Age 55–64 y‡	Age 65–74 y‡	Age 75–84 y‡
mmol/L (mg/dL)	*mm Hg*		*mmol/L (mg/dL)*	*n*	←——— *$/QALY*				———→
4.2–4.9 (160–189)	<95	Nonsmoker	>1.3 (49)	−1	420 000	270 000	230 000	200 000	230 000
	<95	Smoker	>1.3 (49)	0	350 000	290 000	270 000	200 000	210 000
	<95	Nonsmoker	0.9–1.3 (35–49)	0	390 000	220 000	170 000	160 000	180 000
	≥95	Nonsmoker	>1.3 (49)	0	200 000	210 000	160 000	120 000	160 000
	<95	Nonsmoker	<0.9 (35)	1	250 000	150 000	150 000	140 000	160 000
	≥95	Nonsmoker	0.9–1.3 (35–49)	1	190 000	180 000	120 000	100 000	110 000
	≥95	Smoker	>1.3 (49)	1	200 000	220 000	190 000	120 000	130 000
	<95	Smoker	0.9–1.3 (35–49)	1	310 000	210 000	180 000	150 000	160 000
	≥95	Nonsmoker	<0.9 (35)	2	120 000	120 000	110 000	92 000	100 000
	<95	Smoker	<0.9 (35)	2	180 000	140 000	150 000	130 000	140 000
	≥95	Smoker	0.9–1.3 (35–49)	2	160 000	160 000	130 000	96 000	110 000
	≥95	Smoker	<0.9 (35)	3	100 000	110 000	110 000	88 000	95 000
>4.9 (≥190)	<95	Nonsmoker	>1.3 (49)	−1	310 000	170 000	140 000	140 000	160 000
	<95	Nonsmoker	0.9–1.3 (35–49)	0	220 000	120 000	100 000	110 000	130 000
	≥95	Nonsmoker	>1.3 (49)	0	160 000	130 000	94 000	81 000	100 000
	<95	Smoker	>1.3 (49)	0	290 000	180 000	170 000	130 000	150 000
	<95	Smoker	0.9–1.3 (35–49)	1	210 000	120 000	110 000	100 000	120 000
	≥95	Smoker	>1.3 (49)	1	160 000	140 000	110 000	80 000	95 000
	≥95	Nonsmoker	0.9–1.3 (35–49)	1	120 000	96 000	69 000	66 000	81 000
	<95	Nonsmoker	<0.9 (35)	1	120 000	80 000	84 000	89 000	110 000
	≥95	Nonsmoker	<0.9 (35)	2	56 000	56 000	55 000	56 000	70 000
	<95	Smoker	<0.9 (35)	2	100 000	79 000	87 000	87 000	99 000
	≥95	Smoker	0.9–1.3 (35–49)	2	110 000	96 000	78 000	64 000	75 000
	≥95	Smoker	<0.9 (35)	3	54 000	57 000	59 000	55 000	66 000

* QALY = quality-adjusted life-year.
† Not including age.
‡ Add one risk factor for men 45 years of age or older.

Table 4. Cost-Effectiveness of Primary Prevention with a Statin in Women*

Low-Density Lipoprotein Cholesterol Level	Diastolic Blood Pressure	Smoking Status	High-Density Lipoprotein Cholesterol Level	Risk Factors†‡	Cost-Effectiveness				
					Age 35–44 y	Age 45–54 y	Age 55–64 y‡	Age 65–74 y‡	Age 75–84 y‡
mmol/L (mg/dL)	*mm Hg*		*mmol/L (mg/dL)*	*n*	←— *$/QALY* —→				
4.2–4.9 (160–189)	<95	Nonsmoker	>1.3 (49)	−1	1 400 000	620 000	360 000	240 000	250 000
	<95	Smoker	>1.3 (49)	0	1 400 000	690 000	500 000	300 000	250 000
	<95	Nonsmoker	0.9–1.3 (35–49)	0	960 000	360 000	220 000	170 000	180 000
	≥95	Nonsmoker	>1.3 (49)	0	690 000	400 000	200 000	150 000	160 000
	<95	Nonsmoker	<0.9 (35)	1	660 000	270 000	210 000	130 000	150 000
	≥95	Nonsmoker	0.9–1.3 (35–49)	1	460 000	240 000	120 000	100 000	120 000
	≥95	Smoker	>1.3 (49)	1	600 000	420 000	280 000	170 000	160 000
	<95	Smoker	0.9–1.3 (35–49)	1	930 000	390 000	300 000	190 000	170 000
	≥95	Nonsmoker	<0.9 (35)	2	250 000	150 000	100 000	77 000	93 000
	<95	Smoker	<0.9 (35)	2	680 000	320 000	290 000	160 000	140 000
	≥95	Smoker	0.9–1.3 (35–49)	2	390 000	240 000	160 000	110 000	120 000
	≥95	Smoker	<0.9 (35)	3	220 000	170 000	150 000	88 000	94 000
>4.9 (≥190)	<95	Nonsmoker	>1.3 (49)	−1	560 000	420 000	260 000	140 000	150 000
	<95	Nonsmoker	0.9–1.3 (35–49)	0	390 000	230 000	140 000	94 000	110 000
	≥95	Nonsmoker	>1.3 (49)	0	470 000	290 000	160 000	100 000	100 000
	<95	Smoker	>1.3 (49)	0	550 000	480 000	380 000	190 000	150 000
	<95	Smoker	0.9–1.3 (35–49)	1	410 000	270 000	210 000	110 000	110 000
	≥95	Smoker	>1.3 (49)	1	420 000	310 000	220 000	130 000	100 000
	≥95	Nonsmoker	0.9–1.3 (35–49)	1	330 000	160 000	93 000	98 000	73 000
	<95	Nonsmoker	<0.9 (35)	1	370 000	190 000	150 000	86 000	90 000
	≥95	Nonsmoker	<0.9 (35)	2	190 000	110 000	88 000	58 000	61 000
	<95	Smoker	<0.9 (35)	2	410 000	250 000	220 000	120 000	91 000
	≥95	Smoker	0.9–1.3 (35–49)	2	320 000	180 000	130 000	77 000	73 000
	≥95	Smoker	<0.9 (35)	3	190 000	140 000	120 000	73 000	62 000

* QALY = quality-adjusted life-year.
† Not including age.
‡ Add one risk factor for women 55 years of age or older.

stable for women 55 to 74 years of age, and increased by 50% to 200% for women younger than 55 years of age.

Niacin for primary prevention had an estimated cost-effectiveness ratio of less than $100 000 per QALY for most risk subgroups. The inclusion of niacin as an option would worsen incremental cost-effectiveness ratios for primary prevention with a statin by a factor of two or three. Of note, niacin with concurrent modification in diet as an initial therapy is more beneficial yet less costly than step I diet alone.

Using the upper limit of the 95% CI for the coefficients on the effects of LDL and HDL cholesterol levels did not change cost-effectiveness results significantly, but using the lower limit resulted in cost-effectiveness ratios as much as 80% higher than those in the base-case analysis.

A two-way sensitivity analysis including a 50% decrease in drug costs and upper limits of the confidence interval for coefficients on the effects of LDL and HDL cholesterol level resulted in cost-effectiveness ratios that were 40% to 65% lower than those obtained by using base-case assumptions. A three-way sensitivity analysis (one that assumed a 50% decrease in drug costs, included upper limits of the confidence intervals for LDL and HDL cholesterol level effect coefficients, and assumed no time lag between initiation and effect of treatment) resulted in more favorable cost-effectiveness ratios in men 55 to 84 years of age (60% to 75% decrease), women 75 to 84 years of age (60% to 75% decrease), men 45 to 54 years of age (50% to 60% decrease), women 55 to 74 years of age (50% to 60% decrease), and women 45 to 54 years of age (15% decrease). Incremental cost-effectiveness ratios increased by 15% for men 35 to 44 years of age and by 85% for women 35 to 44 years of age because of the improved cost-effectiveness of treatment at older ages.

The benefits of a low-fat diet may be less than those assumed for this analysis (47). If primary prevention with a statin is compared directly with no primary prevention, the incremental cost-effectiveness of primary prevention with a statin would remain relatively stable for the two youngest age groups but would become approximately 20% to 40% more favorable than in the base-case analysis for persons 55 years of age or older.

Results for primary or secondary prevention with

Table 5. Cost-Effectiveness of Secondary Prevention with Simvastatin*

Group	Cost-Effectiveness				
	Age 35–44 y	Age 45–54 y	Age 55–64 y	Age 65–74 y	Age 75–84 y
	←— *$/QALY* —→				
Men	4500	1800	3900	6700	9900
Women	40 000	8100	8400	9500	11 000

* QALY = quality-adjusted life-year.

statins were not very sensitive to assumptions about the number of physician visits (an assumption of no additional physician visits reduced the cost-effectiveness ratio by approximately 10%) or the costs of patient time.

Cost-effectiveness results were somewhat sensitive to assumptions about preference weights for quality of life. If no adjustment was made for quality of life, cost-effectiveness ratios would be reduced by as much as approximately 20% compared with the base-case analysis; however, most ratios remained within 10% of base-case values.

Discussion

Primary Prevention

Cost-effectiveness results for primary prevention with a low-fat diet are consistent with the National Cholesterol Education Program guidelines for most subgroups. For primary prevention, however, the cost-effectiveness results imply that for otherwise healthy young women (those with one or no risk factors), primary prevention with step I diet may not be a cost-effective option.

National Cholesterol Education Program guidelines also recommend drug treatment for all persons with LDL cholesterol levels of 4.9 mmol/L or greater (≥190 mg/dL) and for persons with LDL cholesterol levels of 4.2 to 4.9 mmol/L (160 to 189 mg/dL) and two or more risk factors. For these patients, cost-effectiveness results indicate that primary prevention with a statin may not be cost-effective for some risk subgroups.

There is no clear threshold value that determines when a therapy is or is not cost-effective (48). However, it is informative to discuss our results with respect to several different threshold values. At a cost-effectiveness threshold of $50 000 per QALY, primary prevention with a statin would not be considered cost-effective for any of the 240 risk subgroups. Primary prevention with diet would be considered cost-effective in 159 of 240 risk subgroups at this threshold. The 81 subgroups in which diet would not be considered cost-effective are largely made up of women younger than 55 years of age.

If the cost-effectiveness threshold were $100 000 per QALY, primary prevention with diet would be cost-effective for all but 30 risk subgroups; the exceptions are mostly women younger than 45 years of age and women 45 to 54 years of age with an LDL cholesterol level of 4.2 to 4.9 mmol/L (160 to 189 mg/dL) and fewer than two risk factors. Primary prevention with a statin would be cost-effective for 62 of 240 risk subgroups. In particular, primary prevention with a statin would not be considered cost-effective for women younger than 55 years of age or for most women 55 years of age or older with fewer than three risk factors.

For all of the treatment recommendations of the National Cholesterol Education Panel guidelines to be considered cost-effective, the threshold would have to be $680 000 per QALY.

One could also compare these results to the cost-effectiveness of other currently accepted interventions. For example, the cost-effectiveness in 1995 U.S. dollars for annual screening with a fecal occult blood test for colorectal cancer is estimated at $18 000 per QALY; for annual mammography in women 55 to 65 years of age it is $150 000 per QALY; for single-vessel angioplasty in patients with severe angina it is $7700 to $10 000 per QALY; and for single-vessel angioplasty in patients with mild angina it is $108 000 to $112 000 per QALY (49).

We chose to present the societal perspective. Using alternative perspectives, such as that of the individual patient or a managed care organization, would probably result in different cost-effectiveness ratios, along with different cost-effectiveness thresholds for each perspective. For example, higher-income persons may be willing to pay more than others, whereas managed care organizations might insist on cost-saving.

Although the goal of the National Cholesterol Education Program guidelines is to provide a simple guideline for prescribing physicians, it is important to note that cost-effectiveness ratios vary differentially with individual risk factors. Not surprisingly, if a risk factor has a greater impact on coronary heart disease risk, the cost-effectiveness ratios will reflect this difference. For example, diastolic blood pressure has a greater effect on cost-effectiveness ratios than does smoking status.

To identify the most appropriate candidates for cholesterol-lowering therapy, Avins and Browner (50) proposed a revision to the National Cholesterol Education Program recommendations. They emphasized the importance of advancing age by assigning additional risk for each incremental decade of age above 35 years of age for men and 45 years of age for women (50). This emphasis on age is consistent with our cost-effectiveness findings, although the specific treatment recommendations of these two approaches would depend on the choice of cost-effectiveness thresholds.

Secondary Prevention

Our cost-effectiveness results for secondary prevention with a statin are consistent with the National Cholesterol Education Program guidelines for secondary prevention and with cost-effectiveness results obtained from clinical trials (11). Cost-effectiveness ratios for secondary prevention for all risk subgroups were well within the range considered to be cost-effective. Twenty-nine of the 240 risk subgroups were found to be cost-saving; these subgroups consisted chiefly of male smokers in middle-age groups (45 to 64 years of age). The cost-effectiveness ratios were less than $45 000 per QALY for secondary prevention with a statin in all subgroups.

Limitations

This analysis did not include the effects of diabetes and family history of coronary heart disease, which are included in the National Cholesterol Education Program guidelines. Published estimates of the relative risk for coronary heart disease attributable to diabetes and family history are approximately 1.5 to 1.8 (51) and 1.3 (52), respectively. Including these additional risk factors in this analysis would surely result in more favorable cost-effectiveness ratios for persons who had them.

Costs of treating coronary heart disease are based on data on practice patterns from 1987 (28). Any increase in costs or cost savings resulting from more widespread use of newer treatments are not included.

We recognize that few payers actually pay wholesale price and that many payers, such as large pharmacy benefit management companies or managed care organizations, receive large discounts from wholesale price for their member prescriptions. These discounts were not included in this analysis because there is no good source for these data. Because cost-effectiveness ratios are almost directly proportional to the costs of the statin drugs, rough calculations can be made by the interested reader to estimate the impact of a specific discount known to them.

Cost assumptions for step I diet therapy were based on the National Cholesterol Education Program guidelines and included only costs associated with follow-up physician visits and laboratory tests. In practice, additional costs or cost savings would probably include those associated with substituting lower-fat foods, and patients would be followed only as part of the annual physical examination visit. In addition, the possible benefits of a low-fat diet on conditions other than coronary heart disease were not included.

The results described in this paper apply only to the cost-effectiveness of the National Cholesterol Education Program guidelines for use of statins. For subgroups of patients in which the cost-effectiveness ratios for statin treatment are not favorable, treatment with niacin or bile acid sequestrants may be more (or less) cost-effective. Stinnett and colleagues (8) showed that "stepped care," in which all patients begin treatment with niacin and those who cannot tolerate niacin switch to lovastatin, generally dominates the strategy of starting every person directly on lovastatin therapy. Other cost-effectiveness studies have shown a wide range of cost-effectiveness ratios for cholestyramine therapy (7, 53–56).

We considered pravastatin for primary prevention because it was shown to reduce mortality in a randomized clinical trial (2). The cost-effectiveness of other widely used statin drugs (simvastatin, atorvastatin, cerivastatin, and fluvastatin) in primary prevention remains to be assessed. For example, if the cost per percentage change in lipid level is higher or lower for other statins, the results could differ from those presented here.

Primary prevention with a statin does not look as favorable in our study as in some other analyses because we analyzed its cost-effectiveness assuming not only preexisting secondary prevention but also preexisting primary prevention, in the form of other more cost-effective therapies (such as diet) or ther-

Appendix Table. Effects of Treatment Strategies on Cholesterol Levels*

Author (Reference)	Change in Total Cholesterol Level	Change in High-Density Lipoprotein Cholesterol Level	Change in Low-Density Lipoprotein Cholesterol Level	Patients
	←	%	→	*n*
Primary prevention with step I diet				
Denke (20)	−5.3	−5.5	−6.2	41
Denke and Grundy (21)	−8.1	0.0	−7.8	50
Denke and Grundy (22)	−8.5	2.9	−9.0	26
Wood et al. (23)	−7.8	1.8	−10.7	40
Keenan et al. (24)	0.1	−3.8	−2.8	21
Pooled estimate	−6.5	−0.9	−7.7	178
Primary prevention with a statin				
Shepherd et al. (WOSCOPS) (2)	−20.0	5.0	−26.0	6595
Jukema et al. (REGRESS) (25)	−20.0	10.0	−29.0	885
Salonen et al. (KAPS) (26)	−21.0	−1.9	−27.4	447
Pooled estimate	−20.1	5.2	−26.4	7927
Secondary prevention with a statin				
4S (1)	−25.0	8.0	−35.0	4444

* 4S = Scandinavian Simvastatin Survival Study Group; KAPS = Kuopio Atherosclerosis Prevention Study; REGRESS = Regression Growth Evaluation Statin Study; WOSCOPS = West of Scotland Coronary Prevention Study.

apy in other age groups (such as older persons). For heterogeneous groups of patients, cost-effectiveness results based on average patient characteristics can be misleading when used in policy or treatment decisions. Although our analysis does not capture every consideration that is relevant to an individual patient, by defining risk-factor groups in greater detail than previous studies, we hope that these analyses will be a helpful source of information to those involved in the medical decision–making process.

From Harvard School of Public Health, Boston, Massachusetts; University of Alabama at Birmingham, Birmingham, Alabama; Erasmus University Medical School, Rotterdam, the Netherlands; and University of California, San Francisco, School of Medicine, San Francisco, California.

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Requests for Single Reprints: Milton C. Weinstein, PhD, Harvard Center for Risk Analysis, Harvard School of Public Health, 718 Huntington Avenue, Boston, MA 02115-5924.

Requests To Purchase Bulk Reprints (minimum, 100 copies): Barbara Hudson, Reprints Coordinator; phone, 215-351-2657; e-mail, bhudson@mail.acponline.org.

Current Author Addresses: Ms. Prosser: Department of Ambulatory Care and Prevention, Harvard Medical School, 126 Brookline Avenue, Boston, MA 02215.
Dr. Stinnett: University of Alabama at Birmingham, 330 RPHB, Birmingham, AL 35294-0022.
Ms. Goldman, Mr. Williams, and Dr. Weinstein: Center for Risk Analysis, Harvard School of Public Health, 718 Huntington Avenue, Boston, MA 02115-5924.
Dr. Hunink: Erasmus Medical Center, Box 1738, 3000 DR Rotterdam, the Netherlands.
Dr. Goldman: Department of Medicine, University of California, San Francisco, 505 Parnassus Avenue, San Francisco, CA 94143.

Author Contributions: Conception and design: L. Prosser, A.A. Stinnett, M.C. Weinstein.
Analysis and interpretation of the data: L. Prosser, P.A. Goldman, M.C. Weinstein.
Drafting of the article: L. Prosser.
Critical revision of the article for important intellectual content: P.A. Goldman, M.G.M. Hunink, L. Goldman, M.C. Weinstein.
Final approval of the article: L. Prosser, A.A. Stinnett, P.A. Goldman, L.W. Williams, M.G.M. Hunink, L. Goldman, M.C. Weinstein.
Obtaining of funding: M.C. Weinstein.
Administrative, technical, or logistic support: P.A. Goldman, L.W. Williams.
Collection and assembly of data: L. Prosser, P.A. Goldman.

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