

Maximizing the Cost-effectiveness of Lipid-Lowering Therapy

Terry A. Jacobson, MD; Jeffrey R. Schein, DrPH; Amy Williamson, MPP;
Christie M. Ballantyne, MD

Cardiovascular disease, including coronary heart disease, is the leading cause of death both in men and in women in the United States. The purpose of this review is to describe the effectiveness of lipid-lowering therapy in reducing cardiovascular morbidity and mortality, which has recently been extended to patients with mild to moderate hypercholesterolemia, and the cost of providing therapy, which would be prohibitive if all persons with hypercholesterolemia received treatment. Cost-effectiveness analysis provides a rational means of allocating limited health care resources by allowing the comparison of the costs of lipid-lowering therapy, in particular, therapy with β -hydroxy- β -methylglutaryl-CoA (coenzyme A) reductase inhibitors (statins), with the costs of atherosclerosis that could be prevented by lowering cholesterol. To extend the benefits of treatment to the large number of persons not receiving therapy, we need to implement more cost-effective treatment by improving risk assessment, increasing treatment effectiveness, and reducing the cost of therapy. *Arch Intern Med.* 1998;158:1977-1989

Cardiovascular disease is the leading cause of mortality in the United States, accounting for more deaths than the next 7 leading causes of death combined.¹ It is also the largest source of health care spending.^{2,3} The β -hydroxy- β -methylglutaryl-CoA (coenzyme A) reductase inhibitors (also known as statins) represent a major breakthrough in the prevention of cardiovascular disease through lipid lowering. Despite the proven benefits of statin therapy, if all patients who have high cholesterol were treated with these agents—approximately 12.7 million American adults, as estimated in the most recent National Health and Nutrition Examination Survey (NHANES III)⁴—the national cost borne by private health plans, Medicare, and Medicaid would amount to billions of

dollars.⁵ The real challenge for policymakers, health plan administrators, and health care providers is to determine how to provide the benefits of statin therapy to the greatest number of patients without exploding health care expenditures.

Cost-effectiveness analysis provides a method for addressing this challenge by comparing the costs of treatment with associated patient outcomes. In this Review Article, we use cost-effectiveness methods to compare the clinical promise of lipid-lowering therapy, and the statins in particular, with the economic implications of treatment, in particular, the costs of atherosclerosis that are prevented by cholesterol reduction. First, we discuss the costs associated with coronary and carotid atherosclerosis and review data on the efficacy of lipid-lowering therapies. We then review clinical trial evidence that different statins have similar beneficial effects of slowing the progression of coronary and carotid disease and decreasing coronary events and stroke, consistent with a class effect. Finally, we present evidence on the cost-effectiveness of various cholesterol-lowering therapies and provide suggestions for how to maximize cost-effectiveness.

From the Department of Medicine, Emory University, Atlanta, Ga (Dr Jacobson); Novartis Pharmaceuticals Corporation, East Hanover, NJ (Dr Schein); Lewin-TAG Inc, Boston, Mass (Ms Williamson); and Department of Medicine, Baylor College of Medicine, Houston, Tex (Dr Ballantyne). Dr Jacobson has received speaking and consulting honoraria from Bristol-Myers Squibb Company, Princeton, NJ; Novartis Pharmaceuticals Corporation; Merck & Co Inc, West Point, Pa; and Pfizer Inc, New York, NY. Ms Williamson is a consultant to Novartis Pharmaceuticals Corporation. Dr Ballantyne has received research support within the last 3 years from Novartis Pharmaceuticals Corporation; Merck & Co Inc; Parke-Davis, Morris Plains, NJ; and Pfizer Inc; is a consultant for Novartis and Merck; and is on the speakers' bureau and receives honoraria from Merck, Novartis, Parke-Davis, Pfizer, and Bristol-Myers Squibb.

COST OF ATHEROSCLEROSIS

Most published research on the cost and cost-effectiveness of lipid-lowering therapy focuses on the costs associated with coronary heart disease (CHD) that are avoided by reducing cholesterol levels. Many studies assume a societal perspective, including all outcomes and costs that are related to the disease, regardless of who bears them. Costs include medical resources (such as medications and hospital services) as well as lost productivity of patients (referred to as *indirect costs*) and, in some cases, their caregivers.

About one half of the mortality and one third of the economic cost associated with cardiovascular disease is due to CHD, which is the leading cause of death both in men and in women in the United States.¹ In 1998, approximately 1.1 million Americans will have a myocardial infarction (MI); one third of them will die, and two thirds of those who survive will be left with some extent of permanent disability.¹ According to projections made by the American Heart Association, the direct costs of CHD, including expenditures for hospitals, nursing homes, physicians and other health care professionals, drugs, home health, and other medical durables, amount to an estimated \$51.1 billion, and indirect costs owing to lost productivity increase the total cost of CHD to \$95.6 billion.¹

The clinical consequences of CHD have large cost effects. Wittels et al⁶ used a decision model to evaluate the cost of the 5 primary events related to CHD that were identified in the Framingham Heart Study. Patients were tracked for 5 years after diagnosis or until death. The estimated 5-year costs (in 1986 US dollars) of the events were \$51 211 for acute MI, \$24 980 for angina pectoris, \$40 581 for unstable angina pectoris, \$9078 for sudden death, and \$19 697 for nonsudden death.

The use of revascularization procedures to treat CHD has increased dramatically during the last 15 years. The American Heart Association estimates that approximately 573 000 coronary artery bypass grafting (CABG) procedures and 419 000 percutaneous transluminal coronary angioplasty procedures were performed

in 1995, at an average cost of \$44 820 and \$20 370, respectively.¹

Atherosclerosis also can lead to stroke, which accounts for about 158 000 deaths in the United States each year and is the third leading cause of death after heart disease and cancer.¹ Each year, approximately 600 000 Americans have a stroke, and more than 70% of those who survive have impaired ability to work at an average of 7 years after the event.¹ Stroke is the No. 1 cause of serious disability in the United States.¹ Annual expenditures for stroke have been estimated to be \$17 to 28 billion for direct costs and \$13 to 15 billion for indirect costs.^{1,7} One study estimated that in 1992, mean hospital costs for patients who have had a stroke ranged from \$4600 to \$21 500 (depending on the cerebrovascular subgroup: subarachnoid hemorrhage, intracerebral hemorrhage, ischemic cerebral infarction, transient ischemic attack),⁸ and another estimated the lifetime cost of stroke per person to be \$103 500, including direct and indirect costs.⁹

Clearly, the clinical sequelae of atherosclerosis, as well as the procedures used to treat them, are costly. However, based on the established relation between low-density lipoprotein cholesterol (LDL-C) levels and CHD, which has been well documented in numerous observational epidemiological studies and clinical trials of lipid-lowering therapy, cholesterol-lowering therapy has been proved to reduce coronary mortality and morbidity, although the relation between cholesterol level and stroke is less clear. The development of the statins, which are powerful lipid-regulating agents, has made possible substantial reductions in total cholesterol and LDL-C levels, as well as improvements in high-density lipoprotein cholesterol (HDL-C) and triglyceride levels.

EFFECTIVENESS OF STATIN THERAPY: CLINICAL TRIAL EVIDENCE

Before the availability of statin therapy, agents used to lower cholesterol were plagued by poor compliance of patients to the medication regimen and low efficacy, and early trials of lipid-lowering therapy

did not provide conclusive evidence of a benefit on total mortality, although a meta-analysis of earlier trials showed a significant 13% reduction in CHD mortality ($P < .002$) and a significant 10% reduction in total mortality ($P < .03$) for each 10% reduction in the cholesterol level.¹⁰ With the advent of the statins, greater reductions in LDL-C were achieved as a result of greater efficacy and improved tolerability.

Mechanism of Action and Effects on Lipids

All statins have the same mechanism of action: the inhibition of β -hydroxy- β -methylglutaryl-CoA reductase, the rate-limiting enzyme of cholesterol biosynthesis. The major effect, therefore, is a reduction in the level of LDL-C, caused by enhanced clearance of low-density lipoprotein particles owing to an increased number of low-density lipoprotein receptors in the liver. In addition, there is a modest effect on the triglyceride level, which is primarily due to increased removal of very-low-density lipoprotein and intermediate-density lipoprotein particles.

In general, statin therapy at routine dosages decreases LDL-C levels by 20% to 46% (**Table 1**). The level of HDL-C is typically increased by 5% to 10%, and at commonly used dosages, the triglyceride level is modestly reduced by 10% to 20%, although high-dosage atorvastatin calcium²³ and simvastatin²⁴ have been reported to reduce the triglyceride level by 46% and 33%, respectively, in patients with elevated triglyceride levels at baseline.

Effects on Progression of Coronary and Carotid Disease

During the last several years, a large number of angiographic and ultrasonographic studies have provided evidence that statins produce beneficial effects on the progression of atherosclerotic disease. Angiographic trials of statin therapy have consistently demonstrated substantial reductions in LDL-C levels, reduced progression and even induced regression of CHD, and reduced development of new CHD lesions (**Table 2**). In most of these

trials, which ranged in duration from 2 to 4 years, the minimum lumen diameter was reduced by 0.01 to 0.03

Table 1. Effect of Statins on Low-density Lipoprotein Cholesterol (LDL-C)*

Agent	Dosage, mg/d	Decrease in LDL-C Level, %
Fluvastatin sodium	20 ¹¹	21
	40 ¹¹	26
	80 [†]	32
Pravastatin sodium	10 ¹²	18
	20 ¹³	25
	40 ¹⁴⁻¹⁶	28
Lovastatin	20 ¹⁷	24
	40 ¹⁷	34
	80 ¹⁷	40
Simvastatin	5 ^{12,18-20}	23
	10 ^{12,18-20}	28
	20 ^{12,18-20}	37
	40 ²¹	40
Atorvastatin calcium	10 ²²	38
	20 ²²	46
	40 ²²	51
	80 ²²	54

*Adapted with permission from Blum CB, Stone NJ, Winslow E. Management of Lipids in Clinical Practice. Caddo, Okla: Professional Communications Inc; 1997.

†Administered 40 mg twice daily (Lescol [fluvastatin] [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 1996).

mm per year with treatment, and the development of new CHD lesions was reduced by 40% to 50% with treatment. Ultrasound trials have demonstrated a similar benefit on carotid artery disease (**Table 3**).

Despite the range of mean baseline LDL-C levels in the angiographic statin trials and the different statins used (lovastatin, simvastatin, pravastatin sodium, and fluvastatin sodium), the effect of statin therapy on minimum lumen diameter is remarkably consistent (**Figure 1**), indicating a class effect. The treatment effect calculated by the difference between the change in minimum lumen diameter with a statin and the change in minimum lumen diameter with placebo was 0.03 to 0.08 mm; in most trials, the difference in the minimum lumen diameter change between statin and placebo was 0.06 to 0.08 mm.

A similar benefit on carotid atherosclerosis has been demonstrated in ultrasound trials of statin therapy (Table 3). In trials of lovastatin and pravastatin, comparison of the change in intima-media thickness between treatment groups showed less progression and even regression of carotid atherosclerotic lesions with treatment.

Effects on Coronary Events and Total Mortality

The effect of statins on coronary disease also has been evaluated in trials with clinical events as the primary end point, providing direct information about the effect of treatment on morbidity and mortality due to CHD. Five major clinical event trials, which enrolled a total of 30 817 patients, studied the benefits and risks of 3 different statins (simvastatin, pravastatin, and lovastatin) in a broad range of patients (**Table 4**). Primary and secondary prevention in patients with high levels of LDL-C were studied in the West of Scotland Coronary Prevention Study (WOSCOPS)¹⁵ and the Scandinavian Simvastatin Survival Study (4S),³⁸ respectively, whereas patients with mild to moderate elevations in LDL-C levels were studied in the primary-prevention Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),³⁷ and the secondary-prevention Cholesterol and Recurrent Events trial (CARE)¹⁴ and Long-term Intervention with Pravastatin in Ischaemic Disease study (LIPID).³⁹ All these

Table 2. Effect of Statin Therapy on Coronary Disease: Angiographic Trials^a

Trial	Drug and Dosage, mg/d	Decrease in LDL-C Level, %	LDL-C Level Achieved, mmol/L (mg/dL)	ΔMLD _{PL} – ΔMLD _{DR} , mm	New Lesion Development, ^b %
MARS	Lovastatin, 80	38	2.41 (93)	0.03	↓23 ^c
CCAIT	Lovastatin, 20-80	29	3.15 (122)	0.04	↓53 ^c
Post-CABG	Lovastatin, 40-80 ^d	38	2.40-2.51 (93-97)	0.18 ^e	↓52 ^f
FATS	Lovastatin, 40-80 ^g	46	2.77 (107)	0.06 ^h	NR
MAAS	Simvastatin, 20	31	3.02 (117)	0.08	↓42 ⁱ
PLAC I	Pravastatin sodium, 40	28	3.05 (118)	0.06	↓55 ^c
HARP	Pravastatin sodium, 40 ^j	38	2.23 (86)	0.01	↑50 ^k
REGRESS	Pravastatin sodium, 40	25	3.24 (125)	0.06	NR
LCAS	Fluvastatin sodium, 40 ^l	24	2.87 (111)	0.07	↓41 ^c

^aLDL-C indicates low-density lipoprotein cholesterol; MLD, minimum lumen diameter; PL, placebo; DR, drug; MARS, Monitored Atherosclerosis Regression Study²⁵; CCAIT, Canadian Coronary Atherosclerosis Intervention Trial²⁶; Post-CABG, Post Coronary Artery Bypass Graft²⁷; FATS, Familial Atherosclerosis Treatment Study²⁸; NR, not reported; MAAS, Multicentre Anti-Atheroma Study²⁹; PLAC I, Pravastatin Limitation of Atherosclerosis in the Coronary Arteries³⁰; HARP, Harvard Atherosclerosis Reversibility Project³¹; REGRESS, Regression Growth Evaluation Statin Study¹⁶; and LCAS, Lipoprotein and Coronary Atherosclerosis Study.³²

^bDefined in LCAS as lesions with reference lumen diameter minus MLD less than 0.8 mm at baseline and 0.8 mm or more at follow-up and an increase of 0.4 mm or more in lesion size; in PLAC I as a segment with less than 16% stenosis at baseline that increased by 16% stenosis or more at follow-up; and in MAAS as a segment with 20% or less diameter stenosis at baseline, 20% or more diameter stenosis at follow-up, and an increase of 15% or more in diameter stenosis between baseline and follow-up.

^cAnalyzed by patient.

^dCholestyramine resin, 8 g/d, was added as needed to achieve the treatment goal.

^eIn saphenous vein grafts.

^fMean percentage (modified ratio estimate) of saphenous vein grafts with new lesions per patient.

^gColestipol hydrochloride up to 30 g/d also was assigned to all patients in this treatment group.

^hAnalysis of the worst lesion in each of 9 proximal segments.

ⁱAnalyzed by lesion.

^jSustained-release niacin, 1.5 to 3.0 g/d; cholestyramine, 8 to 16 g/d; and gemfibrozil, 600 to 1200 mg/d also were added as needed to achieve the treatment goal.

^kAnalyzed by vessel

^lCholestyramine up to 12 g/d as tolerated also was assigned to patients with prerandomization LDL-C levels of 4.14 mmol/L (160 mg/dL) or more.

Table 3. Effect of Statin Therapy on Carotid Disease: Ultrasound Trials*

Trial	Drug and Dosage, mg/d	Decrease in LDL-C Level, %	LDL-C Level Achieved, mmol/L (mg/dL)	Δ IMT _{PL} - Δ IMT _{DR} , mm/yr†	
				Mean of Common Carotid, Bifurcation, and Internal Carotid Artery	Common Carotid Artery
ACAPS	Lovastatin, 20-40	25	2.92 (113)	0.015	NA
MARS	Lovastatin, 80	45	2.20 (85)	NA	0.057 (2 y); 0.043 (4 y)
KAPS	Pravastatin sodium, 40	27	3.40 (131)	0.014	0.019
PLAC II	Pravastatin sodium, 10-40	28	3.11 (120)	0.008	0.016

*LDL-C indicates low-density lipoprotein cholesterol; IMT, intima-media thickness; PL, placebo; DR, drug; ACAPS, Asymptomatic Carotid Artery Progression Study³³; MARS, Monitored Atherosclerosis Regression Study³⁴; KAPS, Kuopio Atherosclerosis Prevention Study³⁵; and PLAC II, Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries.³⁶

†Given as 3-year average unless otherwise noted.

studies showed a consistent benefit on relative risk reduction, which ranged from 23% to 36%, without an increase in noncardiovascular deaths. Furthermore, there were no increases in cancers, and the incidence of elevated transaminases greater than 3 times normal and myopathy with statins was similar to the incidence with placebo. The absolute risk reductions varied widely, from 1.8% to 8.5%, because of the marked difference in the cardiovascular event rates in the placebo group. The lowest event rate in patients receiving placebo was observed in patients without CHD and with a mean baseline LDL-C level of 3.89 mmol/L (150 mg/dL) (in AFCAPS/TexCAPS), whereas the highest event rate was in patients with a mean LDL-C level of 4.87 mmol/L (188 mg/dL) and documented CHD (in 4S).

The recently reported AFCAPS/TexCAPS³⁷ highlights the need to study both the relative and absolute risk reduction provided by therapy. This trial included men and women without evidence of CHD or other vascular disease and with relatively low levels of HDL-C, average levels of LDL-C, and a total cholesterol-HDL-C ratio of more than 5. A large number of patients in this trial had borderline-high LDL-C levels that would not require drug therapy by the present US National Cholesterol Education Program (NCEP) guidelines.⁴⁰ Although the study showed an impressive relative risk reduction of 36% for the first acute major coronary event (unstable angina, fatal or nonfatal MI, or sudden cardiac death), 50 patients in this population would need

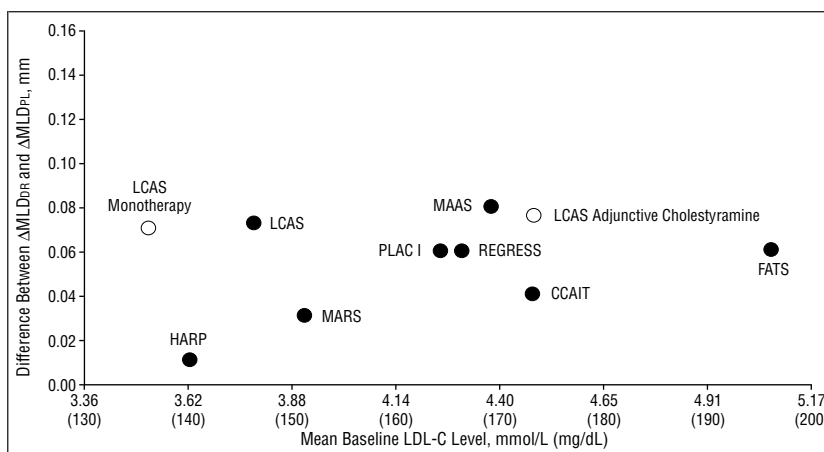


Figure 1. Difference between the change (Δ) in minimum lumen diameter (MLD) in coronary arteries in patients receiving the study drug (MLD_{DR}) and placebo (MLD_{PL}), by mean baseline low-density lipoprotein cholesterol (LDL-C) level, in angiographic trials of statin therapy: lovastatin in the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT)²⁶ and the Monitored Atherosclerosis Regression Study (MARS)²⁵; lovastatin and colestipol hydrochloride in the Familial Atherosclerosis Treatment Study (FATS)²⁸; simvastatin in the Multicentre Anti-Atheroma Study (MAAS)²⁹; pravastatin sodium in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)³⁰ and Regression Growth Evaluation Statin Study (REGRESS)¹⁶; pravastatin with or without niacin, cholestyramine resin, and/or gemfibrozil in the Harvard Atherosclerosis Reversibility Project (HARP)³¹; and fluvastatin sodium with or without cholestyramine (subgroups indicated by open circles) in the Lipoprotein and Coronary Atherosclerosis Study (LCAS).³² Adapted with permission from Herd et al.³² Copyright 1997, Excerpta Medica Inc.

to be treated for 5 years to prevent 1 event.

Thus, lipid-lowering therapy with statins has been shown to provide benefit on CHD progression and events in patients across the full range of LDL-C elevations. In the 2 most recent studies, AFCAPS/TexCAPS and LIPID, conducted in patients with mild to moderate hypercholesterolemia, the LDL-C level was reduced by a modest 25% with statin therapy; however, both trials reported substantial clinical benefit. In certain populations, as in LIPID, marked benefit can result from modest lowering of the LDL-C level, even if the treatment goal is not achieved.

Evidence to Support Guidelines for Treatment

In the NCEP guidelines,⁴⁰ the need for treatment is determined by the LDL-C level, and the goal of treatment is to reduce the LDL-C level to a recommended target, regardless of the percentage of reduction required. In patients with CHD, the guidelines recommend that the level of LDL-C be reduced to 2.59 mmol/L (100 mg/dL) or less.

In support of the NCEP's recommendation to treat to a target LDL-C level, an analysis of 3 trials of statin therapy that enrolled patients with CHD—4S, CARE, and the Post Coronary Artery Bypass Graft Trial—

Table 4. Effect of Statin Therapy on Coronary Disease: Clinical Events Trials*

Trial/Agent	Baseline LDL-C, mmol/L (mg/dL)	Decrease in LDL-C Level, %	LDL-C Level Achieved, mmol/L (mg/dL)	Events at 5 Years	Drug Event Rate	Placebo Event Rate	RRR, %	ARR, %	NNT
Primary prevention									
WOSCOPS†/ pravastatin sodium	5.00 (192)	26‡	4.11 (159)	Nonfatal MI or CHD death	174/3302 (5.3)	248/3293 (7.5)	29	2.2	46
AFCAPS/TexCAPS/ lovastatin	3.89 (150)	25§	2.95 (115)	Nonfatal or fatal MI, unstable angina, or sudden cardiac death as first event	116/3304 (3.5)	183/3301 (5.5)	37	2.0	50
Secondary prevention									
4S simvastatin	4.87 (188)	35	3.15 (122)	Nonfatal MI, coronary death, or resuscitated cardiac arrest	431/2221 (19.4)	622/2223 (28.0)	34	8.5	12
CARE pravastatin sodium	3.60 (139)	32¶	2.53 (98)	Nonfatal MI or CHD death	212/2081 (10.2)	274/2078 (13.2)	24	3.0	34
LIPID† (preliminary)/ pravastatin sodium	3.88 (150)	25#	2.90 (112)	Nonfatal MI or CHD death	554/4512 (12.3)	706/4502 (15.7)	23	3.4	30

*Event rates are given as number of events or number of patients with events/number of patients receiving drug or placebo (percentage). LDL-C indicates low-density lipoprotein cholesterol; RRR, relative risk reduction; ARR, absolute risk reduction; NNT, number needed to treat; WOSCOPS, West of Scotland Coronary Prevention Study¹⁵; MI, myocardial infarction; CHD, coronary heart disease; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study²⁷; 4S, Scandinavian Simvastatin Survival Study²⁸; CARE, Cholesterol and Recurrent Events Trial¹⁴; and LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease study.³⁹

†By number of events.

‡In patients actually treated; LDL-C reduction was 17% in all patients randomized to pravastatin.

§At 1 year.

||By number of patients.

¶Reduction from baseline; 28% reduction compared with placebo.

#Percentage average difference between pravastatin and placebo.

showed that the cardiovascular event rate was directly related to the total cholesterol level achieved during the trial.⁴¹ These data, which were obtained from trials of 3 different statins (simvastatin, pravastatin, and lovastatin), show that different agents in this class have similar benefits in relation to the cholesterol level achieved and support the hypothesis that the cholesterol level achieved, not the percentage of reduction in the cholesterol level, correlates best with event reduction.

Evidence for the appropriate target LDL-C level in patients with CHD was provided by the Post Coronary Artery Bypass Graft Trial, which was conducted in patients who had undergone bypass surgery.²⁷ The LDL-C level was reduced to approximately 2.46 mmol/L (95 mg/dL) with aggressive treatment with 40 to 80 mg/d of lovastatin and to approximately 3.49 mmol/L (135 mg/dL) with moderate treatment with 2.5 to 5.0 mg/d of lovastatin. Patients randomized to receive aggressive treatment had a significant ($P < .001$) 31% reduction in the per-patient percentage of saphenous vein grafts with angiographically documented progression com-

pared with patients randomized to receive moderate treatment, supporting the NCEP's recommended LDL-C treatment goal of 2.59 mmol/L (100 mg/dL) or less for CHD patients.

Inherent in the NCEP guidelines, which do not recommend treating all patients aggressively, is an assumption that there may be less additional benefit of treatment at lower levels of LDL-C. In 316 099 men screened for the Multiple Risk Factor Intervention Trial, followed up for an average of 12 years, the relation between the serum cholesterol level and CHD death was found to be curvilinear, with a steeper slope in the relation between the cholesterol level and CHD mortality at higher cholesterol levels than at lower cholesterol levels.⁴² A 20% difference in the cholesterol level, from 7.76 mmol/L (300 mg/dL) to 6.21 mmol/L (240 mg/dL), decreased the age-adjusted CHD death rate per 10 000 person-years from approximately 35 to 21 deaths per 10 000 person-years, ie, an absolute change in the event rate of approximately 14 per 10 000. In contrast, a 20% decrease in the cholesterol level from 4.65 mmol/L (180 mg/dL) to 3.72

mmol/L (144 mg/dL) decreased the age-adjusted CHD death rate from approximately 11 to 7 deaths per 10 000 person-years, ie, an absolute risk difference of 4 per 10 000. Therefore, the Multiple Risk Factor Intervention Trial screening data suggest that there is less incremental risk at lower cholesterol levels.

In a subset analysis in CARE,¹⁴ there seemed to be a lower threshold of LDL-C below which a reduction in the LDL-C level yielded less additional benefit. The greatest benefit was seen in CARE patients with baseline LDL-C levels of more than 3.88 mmol/L (150 mg/dL), in whom the risk for fatal CHD, nonfatal MI, CABG, or percutaneous transluminal coronary angioplasty was significantly ($P = .008$) reduced by 35%; in patients with baseline LDL-C levels of 3.23 to 3.88 mmol/L (125-150 mg/dL), the risk for these clinical events was significantly ($P < .001$) reduced by 26%. However, among patients with baseline LDL-C levels of less than 3.23 mmol/L (125 mg/dL), there was no statistically significant ($P = .85$) difference in event incidence between treatment groups. The CARE investigators speculated

from this post hoc analysis that 3.23 mmol/L (125 mg/dL) may represent a lower threshold of the LDL-C level for which the initiation of drug therapy influences CHD events. Although recent post hoc analyses from CARE,⁴³ WOSCOPS,⁴⁴ and 4S⁴⁵ have raised questions as to whether additional LDL-C lowering produces additional benefits on CHD events, the relation between event reduction and either LDL-C level achieved or percent LDL-C reduction remains unclear.⁴⁶ Further analyses from the other large trials that enrolled patients with mild to moderate LDL-C elevations, such as LIPID and AFCAPS, may provide additional information on this question of lower threshold for benefit.

Effects on Stroke

In addition to coronary benefits, the benefit of statin therapy on stroke prevention has been studied in 2 recent meta-analyses. These analyses used different criteria for inclusion of trials and therefore included many but not all of the same trials, yet they both demonstrated similar statistically significant reductions in stroke incidence when patients received statin therapy. In 1 meta-analysis, which included 12 trials, the incidence of stroke was significantly reduced by 27% in all trials analyzed ($P = .001$) and by 32% in trials conducted in patients with known CHD ($P = .001$); a 15% reduction in stroke was found in patients without CHD, but this difference was not statistically significant ($P = .48$).⁴⁷ In the other meta-analysis, which included 16 trials, the incidence of stroke was significantly reduced by 29% in all trials (relative risk, 0.71; 95% confidence interval, 0.59-0.86) and by 32% in trials conducted in patients with known CHD (relative risk, 0.68; 95% confidence interval, 0.55-0.85); a 20% reduction in stroke in patients without CHD was not statistically significant (relative risk, 0.80; 95% confidence interval, 0.54-1.16).⁴⁸

COST OF PREVENTION: COST-EFFECTIVENESS OF CHOLESTEROL LOWERING

Although the benefit of cholesterol-lowering therapy on coronary and carotid disease is substantiated by

abundant clinical trial evidence, the cost of treating all patients at risk would be prohibitive. Cost-effectiveness analysis, which compares the differential costs and outcomes of health care interventions, can be used to compare the overall effect of individual treatments for hypercholesterolemia. Cost-effectiveness methods are intended to improve clinical decision making and resource allocation by providing information about the value of alternative treatments.^{49,50} Cost-effectiveness ratios are always incremental because they measure the difference in costs between 2 interventions (a and b), divided by the difference in effectiveness:

$$\begin{aligned} \text{Cost-effectiveness}_{a-b} \\ &= (\text{Cost}_a - \text{Cost}_b) / \\ &(\text{Effectiveness}_a - \text{Effectiveness}_b) \end{aligned}$$

Cost-effectiveness ratios often are expressed in terms of cost per year of life saved (YOLS) or in cost per quality-adjusted YOLS. As such, the ratio indicates how much it costs to gain an additional year of life with one intervention compared with another. Society and its decision makers determine what is a tolerable cost for a year of life by allocating resources to some interventions and not to others. For example, CABG (with cost per YOLS generally <\$30 000) is covered by most health plans, while heart transplantation for patients older than 50 years with terminal heart disease (cost per YOLS, \$100 000) is not. Implicitly, a plan that covers CABG but not heart transplantation considers \$30 000 a reasonable price to pay for a year of life, but considers \$100 000 too high. While there is no consensus on the value of human life, some researchers have argued that treatments that cost less than \$40 000 per YOLS, roughly the cost of renal dialysis, are cost-effective, while those costing more than \$75 000 per YOLS are expensive.^{51,52}

Analyses of the cost-effectiveness of lipid-lowering therapy have generally used models that compare costs and effectiveness of a particular intervention (eg, drug) with no intervention; most of these studies do not include the benefit of reducing the incidence of stroke. These analyses have shown that the cost-effectiveness of lipid-lowering therapy varies widely by age and

other risk factors for CHD, as well as by treatment.

The statins have been shown to be cost-effective for secondary prevention of CHD, particularly for patients who have multiple risk factors. A model by Goldman and colleagues⁵³ found that low-dosage lovastatin was highly cost-effective (<\$20 000 per YOLS, 1989 dollars) for secondary prevention for men and women of all ages with pretreatment cholesterol levels more than 6.46 mmol/L (250 mg/dL), but in patients with CHD and pretreatment cholesterol levels less than 6.46 mmol/L (250 mg/dL), lovastatin was cost-effective for men of all ages (\$16 000-\$38 000 per YOLS) but only for women older than 55 years (up to \$36 000 per YOLS). Ashraf et al⁵⁴ estimated the cost-effectiveness of pravastatin in secondary prevention based on the pooled results of the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries and Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries trials. The model, which was limited to men, was based on differences in clinical outcomes (nonfatal MIs) observed between the pravastatin and placebo groups during the 3-year studies. Framingham Heart Study data were used to project the risk of mortality and long-term morbidity 10 years after an MI. The authors found that pravastatin cost less than \$13 000 per YOLS (1995 dollars) for all men with at least 1 risk factor.

The conclusions on the cost-effectiveness of secondary prevention reached by these models were borne out in an analysis of data collected in 4S. Hospital admissions data were collected prospectively to estimate the effect of simvastatin on hospitalizations for acute cardiovascular events and for coronary revascularization procedures during the median 5.4-year follow-up period.⁵⁵ The study showed that, compared with placebo, a combination of fewer hospitalizations and shorter hospital stays resulted in a 34% reduction ($P < .001$) in the number of hospital days in the simvastatin group. When using US unit costs, this decrease translated into a reduction in hospitalization costs amounting to \$3872 per patient, which lowered the effective cost of

simvastatin therapy by 88% but did not result in overall cost savings when compared with the cost of simvastatin therapy during the 5.4-year period (estimated to be \$4400 per patient). In another analysis of 4S data, in which cost-effectiveness of simvastatin was estimated according to age, sex, and the baseline cholesterol level, the cost of simvastatin therapy per YOLS ranged from \$13 800 to \$27 400, depending on age, sex, and baseline total cholesterol level, when only direct medical costs were considered (1995 dollars).⁵⁶ When the indirect costs of work loss resulting from morbidity were added to the model, the cost of simvastatin ranged from savings for 35-year-old men and women to a cost per YOLS of \$13 300 in a 70-year-old woman.

The cost-effectiveness of the statins is even more dependent on the patient population in the primary prevention of CHD. Goldman et al⁵¹ reported variation in the cost-effectiveness of lovastatin therapy depending on age, sex, and risk factors. Therapy was not cost-effective in any subgroup of women, and only men with particular combinations of risk factors (eg, overweight smokers with high blood pressure) had costs less than \$40 000 per YOLS. By using a model that included the benefits of increasing the HDL-C level, Hamilton et al⁵⁷ found that lovastatin therapy was generally cost-effective for low-risk men aged 40 to 60 years and for low-risk women in their 50s and 60s, with cost-effectiveness ratios of \$28 000 to \$34,000 and \$35 000 to \$44 000, respectively (1992-1993 US dollars). For men in their 30s and 60s, as well as women younger than 50 years, lovastatin therapy was less cost-effective, with cost-effectiveness ratios ranging from \$54 000 to \$120 000. Among high-risk patients, the cost per YOLS for lovastatin therapy among men ranged from \$13 000 to \$33 000. Hay et al⁵⁸ incorporated the indirect benefits of reduced disability days in a model with results that were slightly more favorable to statin therapy. They estimated that, in general, for patients with more than 3 risk factors (including male sex, high blood pressure, smoking habit, diabetes, or

left ventricular hypertrophy), treatment with lovastatin cost less than \$30 000 per YOLS (1989 dollars).

In a comparison of the cost-effectiveness of the statins (excluding atorvastatin, which was not then approved), Martens and Guibert⁵⁹ developed a model for primary prevention that included the benefits of increasing HDL-C levels, based on the Canadian Heart Health Study and the Framingham Heart Study. The model showed that in 45-year-old men who smoke and have pretreatment LDL-C levels of 4.50 mmol/L (174 mg/dL), the cost per YOLS relative to no treatment ranged from \$32 000 with fluvastatin to \$46 000 with pravastatin (1993 US dollars).

When compared with other well-accepted interventions (**Figure 2**), results from these studies show that statins are clearly cost-effective for secondary prevention in almost all patients and for primary prevention in certain subgroups at higher risk for CHD. Thus, the real challenge for the future will be to identify methods to increase the cost-effectiveness of lipid lowering, particularly in primary prevention. In this way, we can extend the clinical benefits of these drugs to even more patients at risk.

IMPROVING COST-EFFECTIVENESS OF LIPID-LOWERING THERAPY

Improving the cost-effectiveness of lipid-lowering therapy is predicated on the premise that clinicians can determine the persons at high risk for CHD, target treatment preferentially toward these persons, and use the most cost-effective therapeutic modalities (**Table 5**). Patients at greatest risk for CHD are those who already have signs of ischemic heart disease, such as clinical signs of angina, MI, abnormal cardiac catheterization results, or extracardiac signs of vascular disease (ie, peripheral vascular disease, abdominal atherosclerosis, or carotid disease). Because secondary prevention is more cost-effective than primary prevention, there is consensus about the absolute need for treatment in secondary prevention in major treatment guidelines in the United States⁴⁰ and Europe.⁶⁰ Primary prevention, on the other hand,

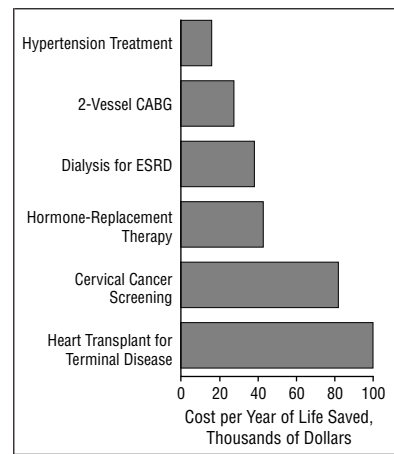


Figure 2. Cost per year of life saved for various medical interventions.⁴⁸ Cost-effectiveness of statin therapy compares favorably with that of other medical interventions. CABG indicates coronary artery bypass grafting; ESRD, end-stage renal disease.

is much more controversial,^{61,62} with many guidelines targeting only those with the highest absolute CHD risk or those with the highest levels of LDL-C. The need for drug treatment should clearly depend on many factors, including aggregate costs of treatment, cost-effectiveness, absolute risk for CHD, and efficacy and safety of treatment.

Primary Prevention: Improving CHD Risk Assessment

Because the prospect of treating all patients at risk on the basis of elevated levels of cholesterol or LDL-C alone would be prohibitively expensive, particularly in today's financial climate, which places a premium on cost consciousness, the contributions of weighted cardiovascular risk factors in addition to cholesterol levels should be considered to improve risk assessment. The risk for CHD can be determined more efficiently by the weighting of additional standardized risk factors rather than simply counting individual risk factors as in the NCEP guidelines.⁴⁰ Although the NCEP guidelines have been useful for their simplicity and as a policy tool to delineate the levels of LDL-C requiring treatment given the number of CHD risk factors, many investigators have advocated more efficient ways to assess the absolute CHD risk, which often require an improved weighting of traditional CHD risk factors.^{63,64} A method for predicting the

Table 5. Improving Cost-effectiveness of Lipid-Lowering Treatment

Target higher-risk patients by improving coronary heart disease (CHD) risk assessment
Use absolute CHD risk threshold of 2% per year
Use newer lipid and nonlipid predictors of CHD (molecular and genetic markers)
Use new technologies: carotid ultrasound, ultrafast computed tomography
Increase treatment effectiveness
Improve compliance
Consider agents (eg, niacin, estrogen) that improve other lipids such as high-density lipoprotein cholesterol, lipoprotein(a), or dense low-density lipoprotein (LDL)
Increase LDL cholesterol reductions with combination therapies
Reduce cost of therapy
Maximize diet, exercise, smoking cessation
Use less expensive drugs (eg, niacin, fluvastatin sodium, estrogen)

absolute CHD risk over a 5- or 10-year period has been developed by the Framingham investigators.^{65,66} Their simple nomogram allows clinicians to calculate more precisely the probability of developing clinical evidence of CHD by incorporating the following 8 risk factors: sex, age, HDL-C level, total cholesterol level, resting systolic blood pressure measurement, cigarette smoking, diagnosis of diabetes, and presence or absence of left ventricular hypertrophy as determined from the electrocardiogram. The relative risk estimates derived from Framingham have been shown to be valid in different populations in the United States⁶⁷ and Europe.⁶⁸ Given the multifactorial nature of CHD risk, a clinician can apply these estimated probabilities of CHD risk to many patients in primary care so as to target the patients with the greatest CHD risk more aggressively. Clear suggestions from the Framingham investigators are that not all risk factors are to be equally weighted and that the groups with the highest absolute risks for CHD are the elderly, patients with diabetes, and patients with left ventricular hypertrophy.

Determining Optimal Threshold Levels of Absolute CHD Risk to Target

In primary prevention, is there a level of absolute CHD risk that clinicians and policymakers can agree to target aggressively, which represents "high-risk" primary prevention? In the revised Canadian guidelines, the intensity of treatment is determined by whether a person's 10-year risk is calculated to be more than 40%, 20% to 40%, 10% to 20%, or less than 10%.⁶⁹ The Task Force of the Euro-

pean Society of Cardiology, European Atherosclerosis Society, and European Society of Hypertension has suggested that patients with a 20% CHD risk for a 10-year interval (2% per year) be targeted for intervention⁶⁰ based on the aggregate cost of such a screening and treatment program and the need to reduce the total numbers of persons requiring treatment. Other investigators⁶¹ favor directing treatment toward persons with a CHD event risk of 3% per year. Although whether the threshold for cost-effective cardiovascular prevention is 1.5%, 2%, or 3% each year is debatable,⁶² the take-home message is that using such cutoffs limits the number of persons needing to be treated with lipid-lowering therapy to prevent 1 CHD morbid or fatal event. By defining such thresholds for treatment, limited resources can be used more cost-effectively, and public policies for treatment can be explicitly debated and discussed. This discussion needs to occur not only among physicians, but also among patients, managed care organizations, governments, and payers (employers).

Analysis of the primary-prevention WOSCOPS⁷⁰ demonstrates that high-risk middle-aged (55-64 years) men had CHD rates higher than 10% for 5 years (2% per year) by having only 1 of the following additional risk factors: minor electrocardiographic abnormalities, pre-existing vascular disease, smoking, an HDL-C level less than 1.10 mmol/L (42.5 mg/dL), hypertension, or a family history of premature CHD. Thus, high-risk men can more easily be identified in this population, and cost-effectiveness of treatment can be maximized. Changing the target

threshold for treatment from 2% per year to 3% per year in the WOSCOPS population would result in a decline of the number needing to be treated to prevent 1 event from 40 persons to approximately 20.⁶¹

In WOSCOPS, as absolute risk increased from 1% per year to 4% per year, the number of patients needing to be treated to prevent 1 coronary event decreased from 66 to 17 persons.⁷⁰ This analysis also compared the benefits of treatment in WOSCOPS with those of the secondary-prevention 4S³⁸ and the Medical Research Council trial of treatment for mild to moderate hypertension (phase V diastolic pressure, 90-109 mm Hg).⁷¹ For men and women aged 35 to 70 years in 4S, the number needing to be treated to prevent 1 probable CHD death or nonfatal MI was only 13. For the prevention of 1 fatal or nonfatal stroke in men aged 45 to 54 years in the Medical Research Council trial, the number needing to be treated was 152, whereas the number of WOSCOPS patients in this age group needing to be treated to prevent 1 CHD death or nonfatal MI was 38. These types of comparisons further demonstrate the concept of targeting persons with the highest absolute risk for CHD as opposed to a given level of cholesterol or blood pressure. In WOSCOPS, the economic implications are clear. If persons in the top 40% of CHD risk were targeted according to the suggested treatment threshold of 2% per year as in the European guidelines, then the number needing to be treated to prevent 1 cardiovascular event would be reduced from 40 to 22, thus greatly improving the cost-effectiveness of therapy.

New CHD Risk Factors. By some estimates, only approximately 30% of all cardiovascular events are attributable to "accepted" risk factors, such as elevated LDL-C levels.⁷² Additional risk factors must exist, and several putative candidates are lipoprotein(a) (Lp[a]), fibrinogen, homocysteine, plasminogen activator inhibitor 1, and C-reactive protein.⁷³ Several epidemiological studies have now looked beyond cholesterol levels and traditional risk factors and have identified novel risk

factors that relate to either thrombus formation or atherosclerotic initiation and progression.

Among the most extensively studied prospectively are fibrinogen and Lp(a). Increased levels of Lp(a) have been shown to be a strong independent risk factor for MI and stroke in some prospective studies⁷⁴ but not in others.⁷⁵ A direct and independent association between plasma fibrinogen levels and the risk for MI or stroke has been established in prospective studies in healthy persons⁷⁶ and in patients with angina.⁷⁷ The plasma level of fibrinogen is associated with risk for ischemic heart disease and severity of atherosclerosis.⁷⁸ Fibrinogen or Lp(a) can easily be added to the existing Framingham equations⁷⁶ to refine the assessment of CHD risk.

Hyperhomocysteinemia has been established as an independent risk factor for early-onset CHD.⁷⁹ Plasminogen activator inhibitor 1 is elevated in the children of men with premature MI, and these elevated plasminogen activator inhibitor 1 levels impair fibrinolytic capacity.⁸⁰ Finally, the most recently described risk factor is C-reactive protein, which may act as a marker of "microinflammation," hypothesized to have a role in the initiation and progression of atherosclerosis. In the Physicians' Health Study, this risk factor increased MI and stroke risk almost 3-fold and was independent of lipid and nonlipid risk factors.⁸¹

New Diagnostic Technologies. The use of new diagnostic modalities also may improve the detection of CHD. Techniques such as carotid ultrasonography⁸² and ultrafast computed tomography^{83,84} have high sensitivity and specificity for detecting CHD. Ultrafast computed tomography, in particular, may be useful in the evaluation of subclinical atherosclerosis in patients without symptoms. The presence of calcifications in the coronary arteries is well correlated with the presence of obstructive coronary disease on angiograms, and ultrafast computed tomography, a relatively noninvasive technique, has high sensitivity in detecting disease (>90%) and a specificity of 40% to 50%.^{85,86} If these new

technologies are further validated in prospective studies, their use in identifying persons at highest CHD risk may increase. However, with their current prices of \$400 to \$500 per scan, their cost would require substantial reduction to justify their use for CHD screening. The US National Heart, Lung, and Blood Institute's Subclinical Cardiovascular Disease Study should help establish which of the new risk factors and diagnostic tests may be useful in conjunction with traditional risk factors in determining which patients are high risk.

Increasing Treatment Effectiveness

Another way to increase the cost-effectiveness of lipid therapy is to enhance the effectiveness of treatment. Enhancing compliance to therapy is pivotal. By the end of the 5-year follow-up in WOSCOPS, more than 30% of patients had dropped out or stopped taking their medication.⁸⁷ Patients who complied with the regimen showed greater declines in CHD, all-cause mortality, and revascularization procedures. Improved outcomes with compliance with the medication regimen have been documented in other cardiovascular interventions.⁸⁸ The issue of compliance with drug therapy and methods to improve compliance in lipid therapy have been reviewed.⁸⁹ In addition, new multidisciplinary efforts to improve compliance will be required to address not only the patient, but also the physician, the allied health care providers, and the health care organization.⁹⁰ The integrity of the physician-patient alliance will still be an integral factor in maximizing compliance by the patient with the medication regimen.

Finally, another method to improve cost-effectiveness is the use of agents that improve constituents of the lipid profile in addition to the LDL-C level. For instance, niacin exerts a favorable influence on the entire lipid profile, including elevating the HDL-C level and decreasing the Lp(a) and dense low-density lipoprotein levels. It has been postulated that increasing the HDL-C level will not only increase cost-effec-

tiveness, but also reduce CHD morbidity and mortality.⁵⁷ On the other hand, niacin can introduce hidden costs because its use may be associated with undesirable cutaneous and gastrointestinal effects that may jeopardize compliance. However, the flushing and rash typical of niacin treatment may be attenuated with the prophylactic use of low-dose aspirin.

Another relatively inexpensive therapy is estrogen,^{91,92} which is the only recognized exogenous agent available in the United States apart from niacin that reduces Lp(a) level. Favorable effects of estrogen on HDL-C and LDL-C levels, as well as on fibrinogen level, no doubt contribute to the cardioprotection exhibited by premenopausal women and postmenopausal women receiving exogenous estrogen. For moderate-risk postmenopausal women, estrogen replacement therapy may represent an alternative to more-expensive statin therapy.

Reducing Cost of Pharmacological Therapy

For CHD risk reduction and lipid-lowering treatments, the effect of nonpharmacological modalities must be maximized. In particular, smoking cessation counseling is highly cost-effective, costing approximately \$200 per YOLS⁵¹—essentially 2 orders of magnitude lower than lipid-lowering regimens or agents directed toward improved blood pressure management. A program of moderate aerobic exercise on the order of 50% to 75% VO_{2max} can improve control of hypertension and dyslipidemia and elevate the HDL-C level. In addition, an earnest attempt to curtail the dietary intake of cholesterol, fat, and saturated fat should be undertaken before resorting to lipid-lowering agents, and such agents should be used in addition to—not instead of—dietary measures.

In contrast to what level of CHD risk to target, consensus exists that, when possible, treatment with less-expensive regimens—including low-dosage combinations—should be undertaken. Most cost-effectiveness analyses of the statins support the premise that drug

acquisition costs account for the majority of the changes in the cost-effectiveness ratios.⁹³ In a sensitivity analysis reported by Goldman's group,⁵³ if the cost of lovastatin were reduced by 40% as the result of a generic formulation, the cost per YOLS would decrease by 30%, and primary prevention with statins would be even more cost-effective. In addition, in a more recent analysis by Hamilton and coworkers⁵⁷ that incorporated changes in both LDL-C and HDL-C levels in the model, a 10% variation in the drug cost of lovastatin was associated with changes of 8% to 9% in the cost per YOLS. Thus, most cost-effectiveness analyses point out the importance of acquisition costs as the major or dominant determinant of the cost-effectiveness of the statins.

The entry dosage of all the existing statins clearly provides the moderate (20%-30%) reductions in the LDL-C level needed by most patients to reach their NCEP goal (Table 1). Data from NHANES III support the notion that the majority of patients with LDL-C levels of more than 3.36 mmol/L (130 mg/dL) can reach NCEP target goals with reductions of the LDL-C level of less than 30%.⁴ In addition to the NHANES III data, clinical trial evidence in both primary prevention (WOSCOPS) and secondary prevention (CARE, LIPID) also suggests that moderate reductions of the LDL-C level in the range of 25% to 28% can result in substantial clinical event reductions, even without the majority of patients reaching NCEP target goals. Although not an a priori hypothesis of the aforementioned trials, the degree of reduction of the LDL-C level beyond 30% was not correlated with any more incremental risk reduction.^{94,95} Thus, all the available statins at their entry dosages seem likely to enable most patients to reach their NCEP goal and to result in clinical CHD risk reduction.

Because the clinical profiles of all the available statins are generally equivalent in terms of efficacy and safety at their entry-level dosages, other factors, such as cost, must be considered when comparing therapy with each of these agents. Cost is especially important

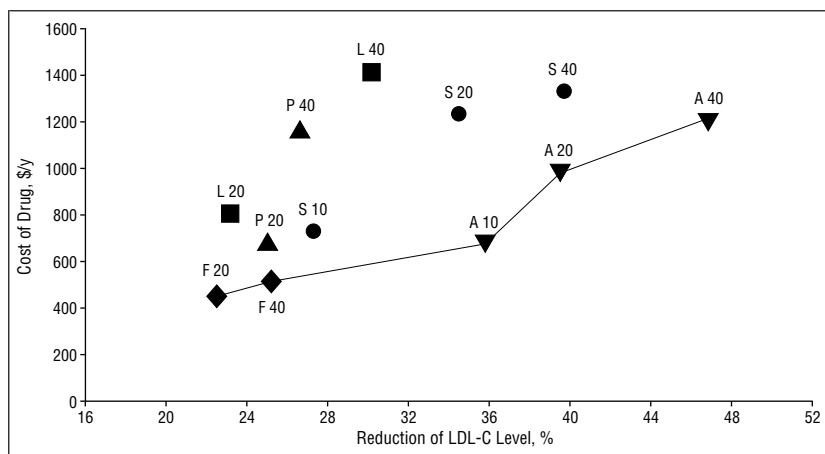


Figure 3. Cost-effectiveness of statin therapy based on the percentage of reduction in the low-density lipoprotein cholesterol (LDL-C) level required. The most cost-effective agents for a given reduction in the LDL-C level define a line called the "cost-efficiency frontier." Any agent above the frontier is less cost-effective (ie, greater cost without greater efficacy). Adapted with permission from Jacobson.⁹³ Copyright 1996, Excerpta Medica Inc. L indicates lovastatin; P, pravastatin sodium; S, simvastatin; A, atorvastatin calcium; and F, fluvastatin sodium. The numbers with the letters indicate the dosage in milligrams per day.

with the statins because many patients will need lifelong therapy. One way to study the issue of cost in cost-effectiveness analysis is to compare the average wholesale price of these agents, which is a nationally published figure. Based on the average wholesale prices, the 30-day average cost for statin therapy ranges from about \$38 for fluvastatin to about \$70 for lovastatin⁹⁶; the monthly cost of the least-expensive statin is about half that of the most-expensive statin. Another approach is to consider the prices that are given to a particular health care organization or managed care organization by various pharmaceutical companies, because these may differ from the average wholesale price.

These cost comparisons are even more striking if drug costs are annualized, indexed according to effectiveness, and expressed as an intermediate end point such as cost per 1% reduction in the LDL-C level. On the basis of this intermediate outcome, fluvastatin and atorvastatin are substantially more cost-effective than lovastatin, pravastatin, or simvastatin: \$18 to \$19 per 1% reduction in the LDL-C level compared with about \$27 to \$35 per 1% reduction for the other statins.⁹⁷ Clearly, for the moderate (20%-30%) reductions of the LDL-C level typically needed by patients with primary hypercholesterolemia, the statin with the lowest acquisition costs (ie, fluva-

statin) seems to be the most cost-effective option, given the current price structure (**Figure 3**). For more-pronounced lowering of the LDL-C level (35%-50%), a higher potency statin, such as atorvastatin, is the most cost-effective alternative. The most cost-effective agents for a given level of LDL-C reduction required are shown in Figure 3. Each health plan can substitute its own prices to determine for itself and its members the most cost-effective agents to use in its formulary, based on its existing price structure and rebates. Several algorithms have been published summarizing the most cost-effective management of hypercholesterolemia in managed care organizations when using a wholesale average pricing structure.^{93,97}

Such cost comparisons gain a further dimension when the effect of dose titration on the cost of therapy is assessed (**Figure 4**). Although the majority of primary-prevention patients achieve target LDL-C levels at the recommended initial dosage of a statin, a small proportion need a higher dosage. At higher dosages of the statins, the cost-effectiveness generally declines, because doubling the dosage of a statin usually adds only 6% more reduction in the level of LDL-C (Table 1), but it increases the costs almost 2-fold (Figure 4). Although greater efficacy is achieved at higher dosages with all the statins, the costs of higher-

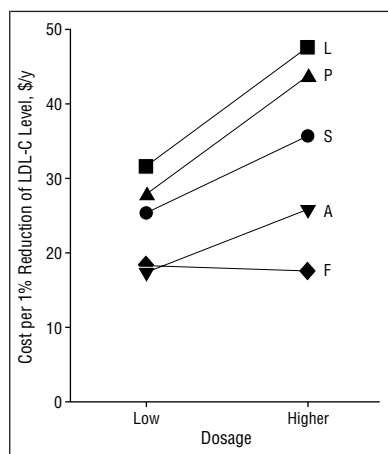


Figure 4. Increasing cost of therapy with statins per 1% reduction in the low-density lipoprotein cholesterol (LDL-C) level as dosage is titrated beyond the typical starting dosage. L indicates lovastatin; P, pravastatin sodium; S, simvastatin; A, atorvastatin calcium; and F, fluvastatin sodium. Reprinted with permission from Jacobson.⁹³ Copyright 1996, Excerpta Medica Inc.

dosage statins are greater when indexed to a 1% reduction in the LDL-C level. To contain the cost of statin therapy for hypercholesterolemic patients in managed care, clinicians may consider using a treatment algorithm based on cost-effectiveness principles. In patients who need a reduction in the LDL-C level of 30% or less, therapy should be initiated with the least-expensive statin. In patients who need a reduction in the LDL-C level of more than 30%, monotherapy with a higher-potency statin such as atorvastatin (or simvastatin) or the combination of a statin with a resin or niacin should be considered.

In terms of cost-effectiveness, the use of generic niacin,⁹⁸ because of its low acquisition cost, is probably the most cost-effective hypolipidemic agent. However, compliance with the medication regimen and tolerability have always plagued acceptance of this agent by patients and physicians, so the lower-priced statins may be preferable. In addition, low-dosage combinations of a statin with less-expensive agents, such as niacin or a bile acid resin, may prove more effective than “pushing the dose” of a given statin, which tends to result in less additional clinical benefit (ie, reduction of the LDL-C level). In 96 patients with moderate elevations of LDL-C, a regimen of low-dosage

colestipol hydrochloride (10 g/d), together with low-dosage (entry-level) lovastatin (20 mg/d), decreased the LDL-C level by 48%, a significantly ($P \leq .001$) greater reduction than the 38% decrease produced by doubling the statin dosage to 40 mg/d.⁹⁹ In this study, low-dosage combinations proved to be more than 25% more cost-effective than higher-dosage statin monotherapy. With the advent of the newer synthetic statins, or when patients expire for the existing drugs, substantial decreases in acquisition costs could result in greater cost-effectiveness and the possibility of treating more patients at risk.

CONCLUSIONS

The clinical trial evidence from the recent randomized controlled trials clearly supports the lipid hypothesis. It is clear that in diverse populations, such as those with or without CHD and those with elevated or “average” levels of cholesterol, large reductions in CHD events are possible, ranging from 25% to 35%. The available data in the most recent trials suggest that this degree of risk reduction is possible for the majority of patients with statin therapy even with only modest reductions in the LDL-C level (ie, 25-30%) and that statins as a group act by class effect. Future research should be directed toward developing not only strategies that provide greater event reduction, but also additional ways to maximize the cost-effectiveness of presently indicated therapy. These issues take on a growing urgency because of the current large gap in treatment of persons with existing CHD or at risk for CHD, with estimates that only 25% to 30% of persons needing therapy actually receive it.¹⁰⁰ This degree of undertreatment persists despite several recent joint position statements by the American Heart Association and the American College of Cardiology on the urgency of treatment.¹⁰¹

In addition to the current treatment gap for dyslipidemia in secondary and primary prevention, recent clinical trials, such as AFCAPS/TexCAPS,³⁷ demonstrate new evidence that a low-risk population with “average” cholesterol levels and no known CHD at baseline also can re-

ceive benefit in CHD event reduction. The results of AFCAPS/TexCAPS may expand the number of patients who benefit from treatment from the 12.7 million Americans estimated in NHANES III⁴ on the basis of the NCEP guidelines by a possible 6 to 8 million additional people.³⁷ With the large growth in patients requiring treatment, more research and tools in cost-effectiveness research will be needed. To extend the benefits of statins to the widest population, answers to the following questions will be crucial: (1) How can we maximize cost-effectiveness in primary prevention through better CHD risk stratification or better determinants of subclinical atherosclerotic disease? (2) Will additional reductions in the LDL-C level beyond the 25% to 30% seen with the initial dosages of the statins result in additional risk reduction or, as with most therapies, result in less additional clinical benefit with higher costs? (3) At what level of absolute CHD risk in primary prevention is it no longer cost-effective (ie, $> \$40,000/\text{YOLS}$) to intervene, given competing uses for health care resources? (4) Can innovative methods be implemented in health care systems or managed care organizations to improve screening, treatment, and compliance with the medication regimen to provide preventive services more effectively? Thus, the challenges of the future will be not only to improve our definitions of the optimal levels of CHD risk and LDL-C levels to target, but also to develop and utilize the newly evolving science of cost-effectiveness, particularly as it relates to maximizing the benefits of lipid-lowering treatment in the prevention of CHD.

Accepted for publication May 26, 1998.

Preparation of the manuscript was sponsored by a nonrestricted educational grant from Novartis Pharmaceuticals Corporation, East Hanover, NJ.

We acknowledge the editorial assistance of Kerrie Jara, MLIS.

Reprints: Terry A. Jacobson, MD, Department of Medicine, Emory University, Thomas Glenn Bldg, 69 Butler St SE, Atlanta, GA 30303 (e-mail: tjaco02@emory.edu).

REFERENCES

- American Heart Association. 1998 Heart and Stroke Statistical Update. Dallas, Tex: American Heart Association; 1997.
- Centers for Disease Control and Prevention. Medical care spending: United States. *MMWR Morb Mortal Wkly Rep*. 1994;43:581-586.
- Hodgson T, Kopstein A. Health care expenditures for major diseases in 1980. *Health Care Financing Rev*. 1984;5:1-12.
- Sempos CT, Cleeman JI, Carroll MD, et al. Prevalence of high blood cholesterol among US adults: an update based on guidelines from the second report of the National Cholesterol Education Program Adult Treatment Panel. *JAMA*. 1993;269:3009-3014.
- Winslow R. Powerful medications for cholesterol pose a paradox for HMOs. *Wall Street Journal*. December 6, 1996:A1, A11.
- Wittels EH, Hay JW, Gotto AM Jr. Medical costs of coronary artery disease in the United States. *Am J Cardiol*. 1990;65:432-440.
- Dobkin B. The economic impact of stroke. *Neurology*. 1995;45(suppl 1):S6-S9.
- Holloway RG, Witter DM Jr, Lawton KB, Lipscomb J, Samsa G. Inpatient costs of specific cerebrovascular events at five academic medical centers. *Neurology*. 1996;46:854-860.
- Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF. Lifetime cost of stroke in the United States. *Stroke*. 1996;27:1459-1466.
- Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: a new look at old data. *Circulation*. 1995;91:2274-2282.
- Peters TK, Muratti EN, Mehra M. Efficacy and safety of fluvastatin in women with primary hypercholesterolemia. *Drugs*. 1994;47(suppl 2):64-72.
- Steinhagen-Thiessen E, for the Simvastatin Pravastatin European Study Group. Comparative efficacy and tolerability of 5 and 10 mg simvastatin and 10 mg pravastatin in moderate primary hypercholesterolemia. *Cardiology*. 1994;85:244-254.
- Lovastatin Pravastatin Study Group. A multicenter comparative trial of lovastatin and pravastatin in the treatment of hypercholesterolemia. *Am J Cardiol*. 1993;71:810-815.
- Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001-1009.
- Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.
- Jukema JW, Bruschke AVG, van Boven AJ, et al, for the REGRESS Study Group. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels: the Regression Growth Evaluation Statin Study (REGRESS). *Circulation*. 1995;91:2528-2540.
- Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) Study results. I: efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. *Arch Intern Med*. 1991;151:43-49.
- Farmer JA, Washington LC, Jones PH, Shapiro DR, Gotto AM Jr, Mantel G, for the Simvastatin and Lovastatin Multicenter Study Participants. Comparative effects of simvastatin and lovastatin in patients with hypercholesterolemia. *Clin Ther*. 1992;14:708-717.
- Douste-Blazy P, Ribeiro VG, Seed M, and the European Study Group. Comparative study of the efficacy and tolerability of simvastatin and pravastatin in patients with primary hypercholesterolemia. *Drug Invest*. 1993;6:353-361.
- Lambrech LJ, Malini PL, for the European Study Group. Efficacy and tolerability of simvastatin 20 mg vs pravastatin 20 mg in patients with primary hypercholesterolemia. *Acta Cardiol*. 1993;48:541-554.
- Zocor (simvastatin) [package insert]. West Point, Pa: Merck & Co; 1996.
- Jones P, Kafonek S, Laurora I, Hunninghake D, for the CURVES Investigators. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol*. 1998;81:582-587.
- Bakker-Arkema RG, Davidson MH, Goldstein RJ, et al. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA*. 1996;275:128-133.
- Davidson MH, Stein EA, Dujovne CA, et al. The efficacy and six-week tolerability of simvastatin 80 and 160 mg/day. *Am J Cardiol*. 1997;79:38-42.
- Blankenhorn DH, Azen SP, Krams DM, et al. Coronary angiographic changes with lovastatin therapy: the Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med*. 1993;119:969-976.
- Waters D, Higginson L, Gladstone P, et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography: the Canadian Coronary Atherosclerosis Intervention Trial. *Circulation*. 1994;89:959-968.
- Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med*. 1997;336:153-162.
- Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990;323:1289-1298.
- MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet*. 1994;344:633-638.
- Pitt B, Mancini GBJ, Ellis SG, Rosman HS, Park J-S, McGovern ME, for the PLAC I Investigators. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol*. 1995;26:1133-1139.
- Sacks FM, Pasternak RC, Gibson CM, Rosner B, Stone PH, for the Harvard Atherosclerosis Reversibility Project (HARP) Group. Effect on coronary atherosclerosis of decrease in plasma cholesterol concentrations in normocholesterolaemic patients. *Lancet*. 1994;344:1182-1186.
- Herd JA, Ballantyne CM, Farmer JA, et al, for the LCAS Investigators. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). *Am J Cardiol*. 1997;80:278-286.
- Furberg CD, Adams HP Jr, Applegate WB, et al, for the Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation*. 1994;90:1679-1687.
- Hodis HN, Mack WJ, LaBree L, et al. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med*. 1996;124:548-556.
- Salonen R, Nyysönen K, Porkkala E, et al. Kuopio Atherosclerosis Prevention Study (KAPS): a population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation*. 1995;92:1758-1764.
- Crouse JR III, Byington RP, Bond MG, et al. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *Am J Cardiol*. 1995;75:455-459.
- Downs JR, Clearfield M, Weis S, et al, for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA*. 1998;279:1615-1622.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
- Tonkin A. Long-term Intervention With Pravastatin in Ischaemic Disease (LIPID). Presented at: the American Heart Association Scientific Sessions; November 12, 1997; Orlando, Fla.
- National Cholesterol Education Program. Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation*. 1994;89:1329-1445.
- Yusuf S, Anand S. Cost of prevention: the case of lipid lowering. *Circulation*. 1996;93:1774-1776.
- Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and differences by age for 316 099 white men. *Arch Intern Med*. 1992;152:56-64.
- Sacks FM, Moyé LA, Davis BR, et al. Relationship between plasma LDL concentrations during drug treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events trial. *Circulation*. 1998;97:1446-1452.
- West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation*. 1998;97:1440-1445.
- Pedersen TR, Olsson AG, Færgeman O, et al, for the Scandinavian Simvastatin Survival Study Group. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation*. 1998;97:1453-1460.
- Grundy SM. Statin trials and goals of cholesterol-lowering therapy. *Circulation*. 1998;97:1436-1439.
- Crouse JR III, Byington RP, Hoen HM, Furberg CD. Reductase inhibitor monotherapy and stroke prevention. *Arch Intern Med*. 1997;157:1305-1310.
- Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. *JAMA*. 1997;278:313-321.
- Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC, for the Panel on Cost-Effectiveness in Health and Medicine. The role of cost-effectiveness analysis in health and medicine. *JAMA*. 1996;276:1172-1177.

50. Freund D, Dittus R. Principles of pharmaco-economic analysis of drug therapy. *Pharmacoeconomics*. 1992;1:20-32.
51. Goldman L, Garber AM, Grover SA, Hlatky MA. Task Force 6: cost effectiveness of assessment and management of risk factors. *J Am Coll Cardiol*. 1996;27:1020-1030.
52. Tengs TO, Adams ME, Pliskin JS, et al. Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal*. 1995;15:369-390.
53. Goldman L, Weinstein MC, Goldman PA, Williams LW. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. *JAMA*. 1991;265:1145-1151.
54. Ashraf T, Hay JW, Pitt B, et al. Cost-effectiveness of pravastatin in secondary prevention of coronary heart disease. *Am J Cardiol*. 1996;78:409-414.
55. Pedersen TR, Kjekshus J, Berg K, et al, for the Scandinavian Simvastatin Survival Study Group. Cholesterol lowering and the use of healthcare resources: results of the Scandinavian Simvastatin Survival Study. *Circulation*. 1996;93:1796-1802.
56. Johannesson M, Jönsson B, Kjekshus J, Olsson AG, Pedersen TR, Wedel H, for the Scandinavian Simvastatin Survival Study Group. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. *N Engl J Med*. 1997;336:332-336.
57. Hamilton VH, Racicot F-E, Zowall H, Coupal L, Grover SA. The cost-effectiveness of HMG-CoA reductase inhibitors to prevent coronary heart disease: estimating the benefits of increasing HDL-C. *JAMA*. 1995;273:1032-1038.
58. Hay JW, Wittels EH, Gotto AM Jr. An economic evaluation of lovastatin for cholesterol lowering and coronary artery disease reduction. *Am J Cardiol*. 1991;67:789-796.
59. Martens LL, Guibert R. Cost-effectiveness analysis of lipid-modifying therapy in Canada: comparison of HMG-CoA reductase inhibitors in the primary prevention of coronary heart disease. *Clin Ther*. 1995;16:1052-1062.
60. Pyörälä K, De Backer G, Graham I, Poole-Wilson P, Wood D, for the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Prevention of coronary heart disease in clinical practice: recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. *Eur Heart J*. 1994;15:1300-1331.
61. Ramsay LE, Haq IU, Jackson PR, Yeo WW, Pickin DM, Payne JN. Targeting lipid-lowering drug therapy for primary prevention of coronary disease: an updated Sheffield table. *Lancet*. 1996;348:387-388.
62. Haq IU, Ramsay LE, Pickin DM, Yeo WW, Jackson PR, Payne JN. Lipid-lowering for prevention of coronary heart disease: what policy now? *Clin Sci (Colch)*. 1996;91:399-413.
63. Kinosian B, Glick H, Garland G. Cholesterol and coronary heart disease: predicting risks by levels and ratios. *Ann Intern Med*. 1994;121:641-647.
64. Grover SA, Palmer CS, Coupall L. Serum lipid screening to identify high risk individuals for coronary death: the results of the Lipid Research Clinics prevalence cohort. *Arch Intern Med*. 1994;154:679-684.
65. Anderson KM, Wilson PWF, Odell PM, Kannel WB. An updated coronary risk profile: a statement for health professionals. *Circulation*. 1991;83:356-362.
66. Kannel WB, D'Agostino RB, Anderson KM, et al. *Coronary Risk and Stroke Prediction Chart and Worksheet*. Dallas, Tex: American Heart Association; 1993.
67. Anderson KM, Odell PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J*. 1991;121:293-298.
68. Laurier D, Nguyen PC, Cazes B, Segond P, and the PCV-METRA Group. Estimation of CHD risk in a French working population using a modified Framingham model. *J Clin Epidemiol*. 1994;47:1353-1364.
69. Frohlich J, Fodor G, McPherson R, Genest J, Langner N, for the Dyslipidemia Working Group of Health Canada. Rationale for and outline of the recommendations of the Working Group on Hypercholesterolemia and Other Dyslipidemias: interim report. *Can J Cardiol*. 1998;14(suppl A):17A-21A.
70. West of Scotland Coronary Prevention Group. West of Scotland Coronary Prevention Study: identification of high-risk groups and comparison with other cardiovascular intervention trials. *Lancet*. 1996;348:1339-1342.
71. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Lancet*. 1985;291:97-104.
72. Heller RF, Chinn S, Pedoe HD, Rose G. How well can we predict coronary heart disease? findings in the United Kingdom Heart Disease Prevention Project. *BMJ*. 1984;288:1409-1411.
73. Ridker PM. Association of hemostatic and thrombotic factors with cardiovascular risk. In: Schafer AI, ed. *Molecular Mechanisms of Hypercoagulable States*. Austin, Tex: Landes Bioscience; 1997.
74. Schaefer EJ, Lamou-Fava S, Jenner JL, et al. Lipoprotein(a) levels and risk of coronary heart disease in men: the Lipid Research Clinics Coronary Primary Prevention Trial. *JAMA*. 1994;271:999-1003.
75. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA*. 1993;270:2195-2199.
76. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease: the Framingham Study. *JAMA*. 1987;258:1183-1186.
77. Thompson SG, Kienast J, Pyke SDM, Haverkate F, van de Loo JCW, for the European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *N Engl J Med*. 1995;332:635-641.
78. de Maat MP, Pietersma A, Kofflard M, Sluiter W, Kluff C. Association of plasma fibrinogen levels with coronary artery disease, smoking and inflammatory markers. *Atherosclerosis*. 1996;121:185-191.
79. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. *JAMA*. 1995;274:1049-1057.
80. Rallidis LS, Megalou AA, Papageorgakis NH, Trikas AG, Chatzidimitriou GI, Tsitouris GK. Plasminogen activator inhibitor 1 is elevated in the children of men with premature myocardial infarction. *Thromb Haemost*. 1996;76:417-421.
81. Ridker PM, Cushman M, Stampfer M, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336:973-979.
82. Kuller L, Borhani N, Furberg C, et al. Prevalence of subclinical atherosclerosis and cardiovascular disease and association with risk factors in the Cardiovascular Health Study. *Am J Epidemiol*. 1994;139:1164-1179.
83. Arad Y, Spadaro LA, Goodman K, et al. Predictive value of electron beam computed tomography of the coronary arteries: 19-month follow-up of 1173 asymptomatic subjects. *Circulation*. 1996;93:1951-1953.
84. Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications: a statement for health professionals from the American Heart Association. *Circulation*. 1996;94:1175-1192.
85. Brundage BH. Beyond perfusion with ultrafast computed tomography. *Am J Cardiol*. 1995;75:69D-73D.
86. Fusman B, Wolfkiel CJ. Ultrafast computed tomography for detection of coronary artery calcification. *Am J Card Imaging*. 1995;9:206-212.
87. Shepherd J, for the WOSCOPS Group. The West of Scotland Coronary Prevention Study (WOSCOPS): benefits of pravastatin therapy in compliant subjects [abstract]. *Circulation*. 1996;94:I-539.
88. McDermott MM, Schmitt B, Wallner E. Impact of medication nonadherence on coronary heart disease outcomes. *Arch Intern Med*. 1997;157:1921-1929.
89. Insull W. The problem of compliance to cholesterol altering therapy. *J Intern Med*. 1997;241:317-325.
90. Houston-Miller N, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action: a statement for healthcare professionals. *Circulation*. 1997;95:1085-1090.
91. O'Brien T, Nguyen TT. Lipids and lipoproteins in women. *Mayo Clin Proc*. 1997;72:235-244.
92. Bush TL. Evidence for primary and secondary prevention of coronary artery disease in women taking oestrogen replacement therapy. *Eur Heart J*. 1996;17(suppl D):9-14.
93. Jacobson TA. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor therapy in the managed care era. *Am J Cardiol*. 1996;78(suppl 6A):32-41.
94. Sacks FM, Moye LA, Davis BR, et al. The influence on coronary events of lipid therapy during treatment with pravastatin: the CARE trial [abstract]. *Circulation*. 1997;96:1-66.
95. Packard CJ. Relationship between LDL-C changes and CHD event reduction with pravastatin in the West of Scotland Coronary Prevention Study (WOSCOPS) [abstract]. *Circulation*. 1997;96:1-107.
96. *Drug Topics Red Book Update*. Montvale, NJ: Medical Economics; July 1998.
97. Jacobson TA. Preventing CHD in the managed care era: improving the cost-effectiveness of lipid lowering therapy. *Am J Managed Care*. 1997;3(suppl):S29-S41.
98. Oster G, Borok GM, Menzin J, et al. Cholesterol-Reduction Intervention Study (CRIS): a randomized trial to assess effectiveness and costs in clinical practice. *Arch Intern Med*. 1996;156:731-739.
99. Schrott HG, Stein EA, Dujovne CA, et al. Enhanced low-density lipoprotein cholesterol reduction and cost-effectiveness by low-dose colestipol plus lovastatin combination therapy. *Am J Cardiol*. 1995;75:34-39.
100. Pearson TA, McBride PE, Miller NH, Smith SC Jr. Task Force 8: organization of preventive cardiology service. *J Am Coll Cardiol*. 1996;27:1039-1047.
101. Grundy SM, Balady GJ, Criqui MH, et al. When to start cholesterol-lowering therapy in patients with coronary heart disease: a statement for healthcare professionals from the American Heart Association Task Force on Risk Reduction. *Circulation*. 1997;95:1683-1685.