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Projected Life-Expectancy Gains With Statin Therapy for Individuals With Elevated C-Reactive Protein Levels

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OBJECTIVES We sought to estimate the potential gains in life expectancy achieved with statin therapy for individuals without overt hyperlipidemia but with elevated C-reactive protein (CRP) levels.

BACKGROUND Persons with low-density lipoprotein (LDL) cholesterol levels below current treatment guidelines and elevated CRP levels are at increased risk of cardiovascular disease and may benefit from statin therapy.

METHODS We constructed a decision-analytic model to estimate the gains in life expectancy with statin therapy for individuals without overt hyperlipidemia but with elevated CRP levels. The annual risks of myocardial infarction (MI) and stroke, as well as the efficacy of statin therapy, were based on evidence from randomized trials. Estimates of prognosis after MI or stroke were derived from population-based studies.

RESULTS We estimated that 58-year-old men and women with CRP levels ≥0.16 mg/dl but LDL cholesterol <149 mg/dl would gain 6.6 months and 6.4 months of life expectancy, respectively, with statin therapy. These gains were similar to those for patients with LDL cholesterol ≥149 mg/dl (6.7 months for men and 6.6 months for women). In sensitivity analyses, we identified the baseline risk of MI and the efficacy of statin therapy for preventing MI as the most important factors in determining the magnitude of benefit with statin therapy.

CONCLUSIONS Our results suggest that individuals with elevated CRP levels, many of whom do not meet current National Cholesterol Education Program guidelines for drug treatment, may receive a substantial benefit from statin therapy. This analysis supports a crucial need for direct intervention trials aimed at subjects with elevated CRP levels. (J Am Coll Cardiol 2002;40: 49–55) © 2002 by the American College of Cardiology Foundation

Current use of statins in the primary prevention of cardiovascular disease is largely limited to those with low-density lipoprotein (LDL) cholesterol levels >160 mg/dl (1). However, half of all heart attacks and strokes occur among individuals classified as having low to moderate risk according to lipid screening alone.

One approach to improving global risk assessment and targeting certain patients for statin therapy includes evaluation of C-reactive protein (CRP) (2), an emerging inflammatory biomarker that is a strong independent predictor of future vascular risk among apparently healthy men and women (3–7). This approach also has pathophysiologic appeal, as the magnitude of benefit of statin therapy appears to be greater among individuals with elevated CRP levels (8,9). Furthermore, several studies indicate that statin therapy reduces CRP levels, independent of its LDL cholesterol-lowering effect (10–14).

The clinical impact of these data is likely to be greatest in primary prevention, where it has recently been demonstrated that statins are highly effective in reducing the risk of first coronary events among those with relatively low lipid levels but elevated CRP levels (13). However, despite the potential for CRP screening to identify individuals with LDL cholesterol levels below current treatment guidelines who might still benefit from statin therapy, the overall impact of treating this large segment of the population is unknown. To address this question, we used a decision-analytic model (15) to estimate the potential life-expectancy gains with statin treatment in the general population classified according to LDL cholesterol and CRP levels.

METHODS

We constructed a Markov state-transition model to simulate hypothetical cohorts of men and women over their lifetime, where the annual events of interest were myocardial infarction (MI), stroke and death. The cohorts were defined according to median LDL cholesterol and CRP levels in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), to create three distinct groups: 1) LDL cholesterol <149 mg/dl and CRP <0.16 mg/dl (low LDL/low CRP); 2) LDL cholesterol <149 mg/dl and CRP ≥0.16 mg/dl (low LDL/high CRP); and 3) LDL cholesterol ≥149 mg/dl (high LDL; this group included subjects with both high and low CRP levels). For each group, we compared statin therapy with no treatment (assuming all groups were receiving dietary counseling).

In the simulation, subjects free of MI and stroke were assigned to either statin therapy or no therapy. Each year, individuals could experience no event, have a fatal or

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Abbreviations and Acronyms

AFCAPS/TexCAPS	= Air Force/Texas Coronary Atherosclerosis Prevention Study
CAPRIE	= Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events
CARE	= Cholesterol and Recurrent Events
CRP	= C-reactive protein
HDL	= high-density lipoprotein
LDL	= low-density lipoprotein
MI	= myocardial infarction
WOSCOPS	= West of Scotland Coronary Prevention Study

nonfatal MI or have a fatal or nonfatal stroke, or they could die of other causes. The base-case analysis was for 58-year-old men (a representative patient in AFCAPS/TexCAPS) (16). All analyses were performed using the decision-analytic program DATA (Treeage Software, Inc., Williamstown, Massachusetts).

Data and assumptions. The probabilities used in our model are shown in Table 1.

Risk of MI. The overall annual incidence of MI observed in AFCAPS/TexCAPS were 5.6 per 1,000 person-years (16). We assumed that this rate was applicable to men aged 55 to 64 years. In a recent analysis of the AFCAPS/TexCAPS population, the risk of MI in subjects with either high LDL cholesterol or high CRP was approximately twice that of individuals with low LDL cholesterol and low CRP (13). Based on the reported relative risks among the LDL/CRP groups, we split the overall MI rate into group-specific rates. For example, we calculated that the annual incidence of MI for individuals with low LDL cholesterol and low CRP was 2.9 per 1,000 person-years. We adjusted these rates by age and gender according to data from national population-based studies (17,18). The efficacy of statin therapy in AFCAPS/TexCAPS was shown to be similar in subjects with either high LDL cholesterol or high CRP. However, no benefit was shown for individuals with low LDL cholesterol and low CRP in that trial (relative risk of 1.08 for statin therapy versus dietary counseling; 95% confidence interval 0.56 to 2.08) (13).

Risk of stroke. We calculated an overall annual incidence of stroke of 2.0 per 1,000 person-years from a weighted average of the rates observed in the control groups of nine randomized trials in the primary prevention of stroke (0.002) (19–27). We assumed that this rate was applicable to men age 55 to 64 years, and we split this rate into group-specific rates based on the relative risks of stroke by CRP levels estimated from the Physicians' Health Study (3). We further adjusted the stroke rates on the basis of age- and gender-stratified population data (28). We assumed

Table 1. Baseline Probabilities and Assumptions

Variable	Base Case	Range	Reference
Risk of MI in low LDL/low CRP group*			
Men	0.00074–0.00610	0.5–3.0 × base case	(16–18)
Women	0.00018–0.00427		
Relative risk of MI†			
Low LDL/high CRP	2.17	1.3–3.9	(13)
High LDL/low CRP	2.17	1.3–3.9	
High LDL/high CRP	2.37	1.4–4.2	
Efficacy of statin therapy for prevention of MI (% reduction)			
Low LDL/low CRP	0	0–20	
High LDL or high CRP	45	30–60	(13)
Fatal MI rate*			
Men	0.031–0.509	0.5–2.0 × base case	(34,35)
Women	0.023–0.455		
Yearly mortality after MI*			
Men	0.014–0.099	0.5–2.0 × base case	(34,35)
Women	0.011–0.108		
Risk of stroke in low LDL/low CRP group*			
Men	0.00017–0.0087	0.5–3.0 × base case	(19–27)
Women	0.00017–0.0057		
Relative risk of stroke			
High CRP‡	1.3	1.1–2.0	(3,6)
Efficacy of statin therapy for stroke prevention (% reduction)			
All subgroups	10	5–30	(19)
Fatal stroke rate*	0.1–0.2	0.5–2.0 × base case	(19,36)
Yearly mortality after stroke (ratio)	2.67	0.5–2.0 × base case	(36)
Efficacy of statins for stroke prevention after MI	0.22	0.1–0.5	(31,32)
Increased risk of stroke after MI§	1.5/4.0	1–5	(31)
Increased risk of MI after stroke§	1.4/2.36	1–5	(33)

*Risk is age-specific; ranges shown are for ages 35 to 85 years. †Relative to low LDL/low CRP group. ‡Relative to low CRP, independent of LDL cholesterol. §Relative risk of nonfatal event/fatal event.

CRP = C-reactive protein; LDL = low-density lipoprotein; MI = myocardial infarction.

Table 2. Age-Specific Gains in Life Expectancy Resulting From Statin Therapy in Men and Women in the Low LDL/High CRP Group

Outcome	Men					Women				
	Age (yrs)					Age (yrs)				
	35	45	55	65	75	35	45	55	65	75
Life expectancy without treatment (yrs)	38.60	29.93	21.88	14.96	9.51	44.77	35.43	26.57	18.69	12.16
Gain in life expectancy with treatment (months)	10.2	9.4	7.4	5.3	3.4	7.9	7.7	7.0	5.8	3.8

Abbreviations as in Table 1.

that LDL cholesterol levels did not predict the risk of stroke (29,30). The efficacy of statin therapy for stroke prevention, on the basis of the CRP levels, is not known. Thus, we assumed the benefit observed in the West Of Scotland Coronary Prevention Study (WOSCOPS) for stroke prevention (10%) was applied to all subgroups (19).

Stroke after MI. The overall risk of stroke after MI was increased according to the rates observed in the Cholesterol And Recurrent Events (CARE) trial (31). We assumed that all patients would receive statin therapy after MI, regardless of their initial treatment strategy, and that statins would reduce the risk of stroke after MI by 22% (31,32).

MI after stroke. The overall risk of MI after stroke was increased according to the rate observed for this subgroup of patients in Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial (33). We assumed that all patients with LDL cholesterol ≥149 mg/dl would receive statin therapy after their stroke, and that the relative risks and efficacy estimates for MI by LDL cholesterol and CRP levels were equivalent to those of stroke-free individuals.

Mortality. We used the Coronary Heart Disease Policy Model to estimate the rate of fatal MI (within one year), adjusted for age and gender, and the subsequent annual coronary heart disease-specific mortality rates, adjusted for age and gender (34). The Coronary Heart Disease Policy Model is a deterministic, population-based, computer stimulation model that incorporates available epidemiologic and clinical data (35).

Stroke-specific mortality, adjusted for age, was calculated based primarily on data from WOSCOPS (19,36). In the absence of published data, we assumed that the stroke fatality rates for patients age 35 to 54 years were the same as for those age 55 years.

Mortality rates due to other causes, specific for age and gender, were based on U.S. life tables (37).

RESULTS

Based on our model, we projected that 58-year-old men with LDL cholesterol <149 mg/dl and CRP ≥0.16 mg/dl would live an average of 19.7 years without treatment and 20.3 years with statin therapy, yielding a life-expectancy gain of 6.6 months. We projected that the life expectancy for 58-year-old women with LDL cholesterol <149 mg/dl and CRP ≥0.16 mg/dl was 24.1 years without treatment and 24.7 years with statin therapy, yielding a life-expectancy gain of 6.4 months. These life-expectancy gains were similar to those observed for 58-year-old men and women with LDL cholesterol ≥149 mg/dl (6.7 months for men and 6.6 months for women). In contrast, statin therapy for men and women in the low LDL/low CRP group resulted in only a modest gain in life expectancy (0.6 months for men and 0.6 months for women).

Projected life-expectancy gains for men and women in the low LDL/high CRP group are shown by age in Table 2. Life-expectancy gains decline with increasing age because of the decline in the number of years of remaining life expectancy. Compared with women of the same age, younger men have a greater gain in life expectancy with statin therapy, reflecting the greater differences in the risk of MI and stroke between men and women at younger ages. However, with increasing age, the benefits in life expectancy observed with statin treatment are slightly greater in women than in men, reflecting the increased rates of cardiovascular disease in postmenopausal women and the longer life expectancy for women overall.

Sensitivity analyses. We performed sensitivity analyses to assess whether our results were stable when clinically plausible variations were introduced in our base-case baseline probabilities and assumptions. Our results were most sensitive to the rate of MI and the efficacy of statin therapy in reducing the risk of MI. Figure 1 shows a two-way sensitivity analysis of the baseline rate of MI (varied from 0.5 to 3 times the base-case values) and the efficacy of statin therapy for reducing MI (varied from 30% to 60%) in subjects with low LDL cholesterol and high CRP. As the rate of MI increases and the efficacy of statin therapy for reducing MI increases, the life-expectancy gains with statin therapy increase. Based on these two variables, the life-expectancy gains with statin therapy ranged from 2.5 months (least favorable assumptions) to 18 months (most favorable assumptions). The magnitude of this effect was similar for men and women.

Our results were moderately sensitive to the annual mortality rate after MI, the efficacy of statin therapy for prevention of stroke and the annual risk of stroke (Fig. 2). Modifying the other variables in our model within clinically plausible ranges resulted in variations in life-expectancy gains of <2 weeks.

The relative risk of the groups with either high LDL cholesterol or high CRP, compared with the low LDL/low CRP group, was comparable to that in AFCAPS/TexCAPS (13). To create a bias against a benefit for

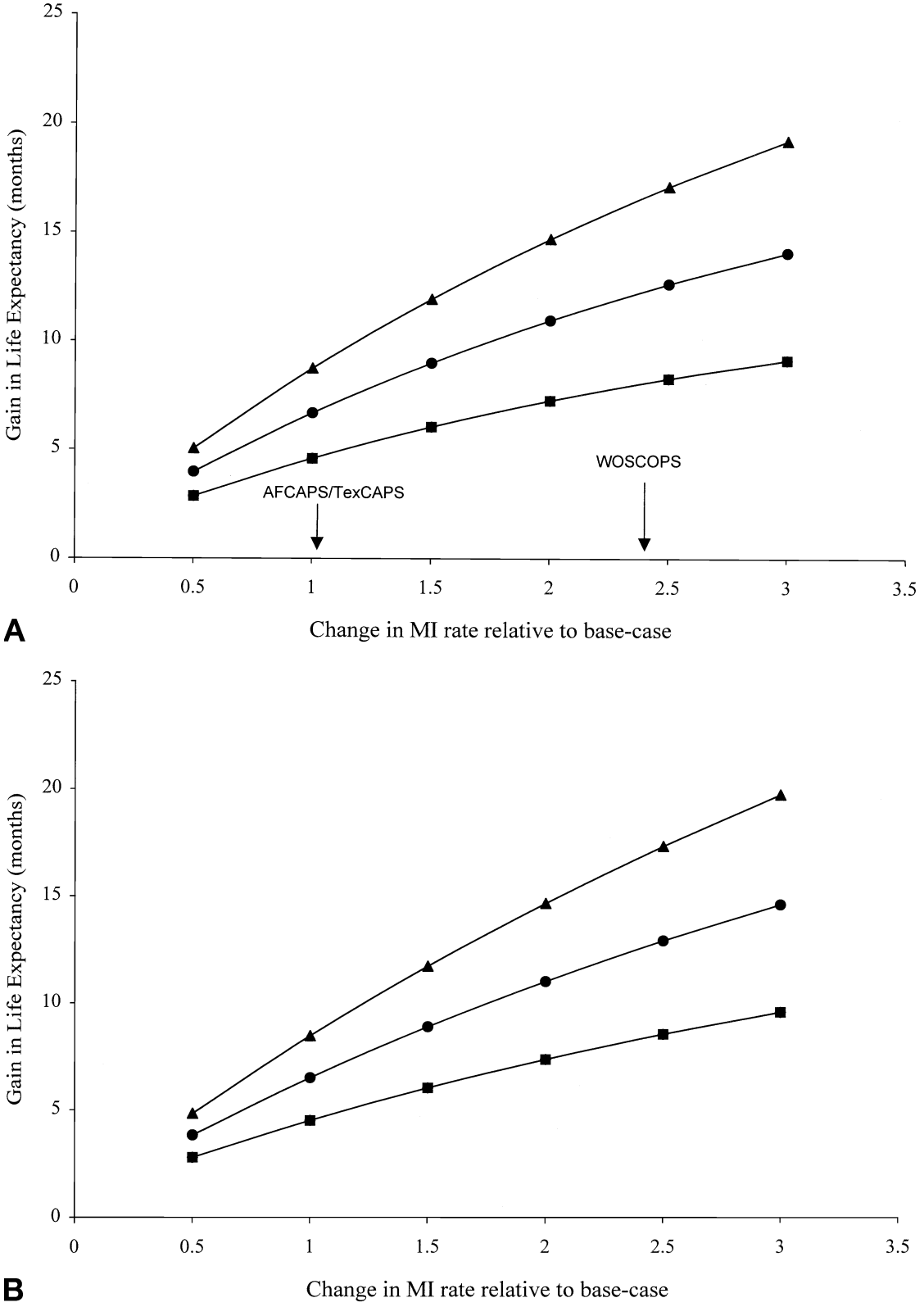

Figure 1. Gains in life expectancy among men **(A)** and women **(B)** in the low-density lipoprotein (LDL)/high C-reactive protein (CRP) group, according to the rate of myocardial infarction (MI) and efficacy of statin therapy for the prevention of MI in the low LDL/high CRP group. **Line with triangles** = 60% efficacy; **line with circles** = 45% efficacy; **line with squares** = 30% efficacy. AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study.

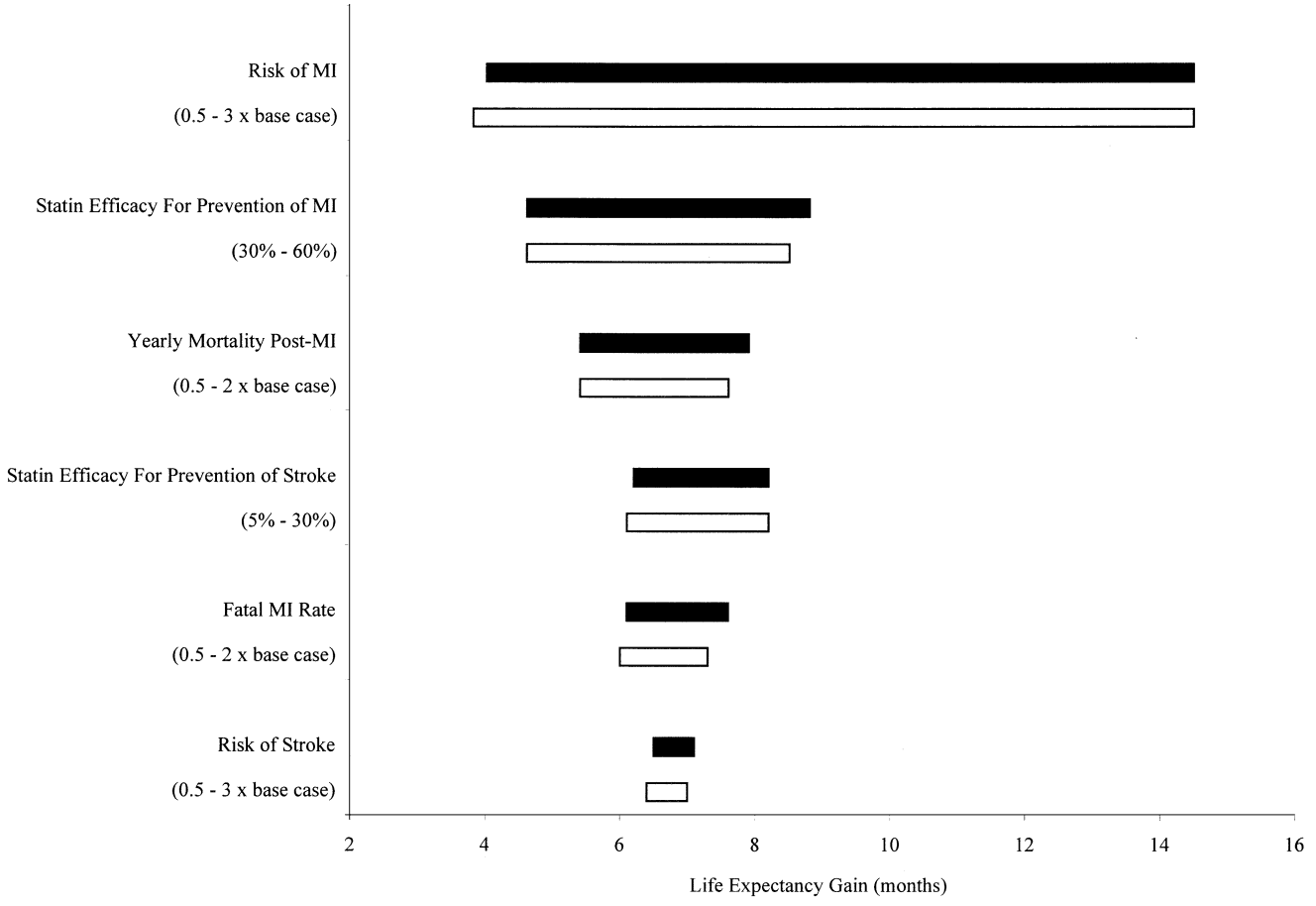

Figure 2. Results of sensitivity analysis. Each **bar** indicates the effect on estimated gains in life expectancy associated with statin therapy in 58-year-old men and women in the low-density lipoprotein (LDL)/high C-reactive protein (CRP) group, when a range of different values (shown in **parentheses**) is used for the indicated variables. The results for men are shown by **solid bars** and the results for women by **open bars**. MI = myocardial infarction.

subjects in the low LDL/high CRP group, compared with the high LDL cholesterol group, we performed sensitivity analyses in which the relative risks of MI and stroke for the low LDL/high CRP group were reduced to 1.3 and 1.1, respectively, and the relative risks of MI and stroke for the high LDL cholesterol group were increased to 4 and 2, respectively. This resulted in projected life-expectancy gains of 3.5 months and 3.4 months, respectively, for men and women in the low LDL/high CRP group and gains of 8.2 months and 8.2 months, respectively, for men and women in the high LDL cholesterol group.

Although the analysis from AFCAPS/TexCAPS showed no benefit of statin therapy in the low LDL/low CRP group, if the efficacy of statin therapy for preventing MI in this group was increased to 20%, the life-expectancy gains for subjects with low LDL cholesterol and low CRP would be 1.9 months for both 58-year-old men and women.

DISCUSSION

We sought to estimate the potential gains in life expectancy achieved with statin therapy for subjects without overt hyperlipidemia but with elevated CRP levels. Our analysis suggests that the projected life-expectancy gain with statin therapy for 58-year-old men and women with LDL cholesterol <149 mg/dl and elevated CRP levels is approximately 6.5 months, which is similar to that for treating patients with LDL cholesterol ≥149 mg/dl.

Our results can be placed in the context of the projected life-expectancy gains demonstrated with other primary preventive strategies (38). As shown in Table 3, the gains predicted with statin therapy for 35-year-old men and women in the low LDL/high CRP group are similar to those previously reported for fundamental interventions in the primary prevention of cardiovascular disease, such as smoking reduction, treatment of hypertension and cholesterol reduction (39), and are greater than those reported for cancer screening programs for the general population (38).

Our results were most sensitive to changes in the baseline rate of MI and the efficacy of statin therapy for preventing MI. Our baseline rate of MI was taken from AFCAPS/TexCAPS (16). The AFCAPS/TexCAPS cohort had low high-density lipoprotein (HDL) cholesterol levels, which represents a potential limitation of our study. Nevertheless, the AFCAPS/TexCAPS cohort was a relatively low-risk group. For example, only 12.5% were current smokers, 2.5% were taking oral treatment for diabetes, 22% were hyper-

Table 3. Gains in Life Expectancy With Various Preventive Interventions

Disease and Intervention	Gain in Life Expectancy (months)	
	Men	Women
Cardiovascular disease		
Targeted therapy for individuals at risk*		
Statin therapy for low LDL/high CRP	10.2	7.9
Achievement of 20% cessation rate among smokers†	5.5	6.7
Reduction in diastolic blood pressure to 88 mm Hg if 90–94 mm Hg†	13.2	10.8
Reduction in total cholesterol†		
to 200 mg/dl if 200–239 mg/dl	6.0	4.8
to 200 mg/dl if 240–299 mg/dl	20.4	18.0
Cancer prevention in individuals at average risk		
10 years of biennial mammography for 50-year-old women‡	NA	0.8
Pap smear every 3 years for 55 years for 20-year-old women‡	NA	3.1
Annual fecal occult-blood test, plus barium enema or colonoscopy every 5 years for 25 years for 50-year-olds‡	2.5	2.2

*For 35-year-old subjects. †Data are from Tsevat et al. (39). ‡Data are from Wright and Weinstein (38). Abbreviations as in Table 1.

tensive and 17% were taking prophylactic aspirin. In comparison, the overall rate of MI was over twofold higher in WOSCOPS (19). As shown in Figure 1 the predicted life-expectancy gains would be even larger if a higher risk group, as reflected by a higher baseline rate of MI, was considered.

Assumptions. Our model involves other assumptions. Because the benefit of statin therapy in AFCAPS/TexCAPS were similar in the low LDL/high CRP and high LDL cholesterol groups (13), we assumed an average effect across these groups. However, our sensitivity analyses showed that even if the benefit in the low LDL/high CRP group was reduced to 30%, 58-year-old men and women still gain 4.6 months of life expectancy with statin therapy.

We assumed a class effect for statin therapy in our analysis (10–14). However, if future clinical studies show that some statins have more potent anti-inflammatory effects, or that more aggressive LDL cholesterol reduction leads to increased risk reduction, then our projected life-expectancy estimates of a benefit from therapy would be conservative.

Conclusions. The clinical benefits anticipated with statin therapy for subjects with LDL cholesterol levels <149 mg/dl with elevated CRP levels may apply to a large proportion of adults in the U.S. The target population and projected gains in life expectancy would be similar or even larger if statin treatment was given to those with elevated CRP levels and LDL cholesterol <160 mg/dl, many of whom do not currently meet National Cholesterol Education Program guidelines (1) for statin therapy for the primary prevention of cardiovascular disease. Thus, our analysis suggests that there may be substantial value in screening for CRP in subjects with LDL cholesterol <160 mg/dl, supporting the need for randomized trials to directly address the benefits of statin therapy in individuals without overt hyperlipidemia.

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REFERENCES

1. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
2. Ridker PM. High-sensitivity C-reactive protein (hs-CRP): a potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001;103:1813–8.
3. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–9.
4. Koenig W, Sund M, Frohlich M, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 1999;99:237–42.
5. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. Am J Epidemiol 1996;144:537–47.
6. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836–43.
7. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 2000;321:199–204.
8. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. Circulation 1998;98:839–44.
9. Horne BD, Muhlestein JB, Carlquist JF, et al. Statin therapy, lipid levels, C-reactive protein and the survival of patients with angiographically severe coronary artery disease. J Am Coll Cardiol 2000;36:1774–80.
10. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. Circulation 1999;100:230–5.
11. Standberg TE, Vanhanen H, Tikkanen MJ. Effect of statins on C-reactive protein in patients with coronary artery disease. Lancet 1999;353:118–9.

12. Ridker PM, Rifai N, Lowenthal SP. Reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. Circulation 2001;103:1191–3.
13. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001;344:1959–65.
14. Albert M, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels. The Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001;286:64–70.
15. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13:322–38.
16. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of the AFCAPS/TexCAPS. JAMA 1998; 279:1615–22.
17. U.S. Department of Health and Human Services. The Framingham Study: an epidemiological investigation of cardiovascular disease—some risk factors related to the annual incidence of cardiovascular disease and death using pooled repeated biennial measurements: Framingham Heart Study, 30-year follow-up. Section 34, NIH Publication 87-2703. Bethesda, MD: National Heart, Lung and Blood Institute, 1987.
18. Elveback LR, Connolly DC, Melton LT 3rd. Coronary heart disease in residents of Rochester, Minnesota. VII. Incidence, 1950 through 1982. Mayo Clin Proc 1986;61:896–900.
19. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333: 1301–7.
20. Wilhelmsen L, Berglund G, Elmfeldt D, et al. The multifactor primary prevention trial in Goteborg, Sweden. Eur Heart J 1986;7: 279–88.
21. Hjermann I, Velve Byre K, Holme I, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease: report from the Oslo Study Group of a randomised trial in healthy men. Lancet 1981;2:1303–10.
22. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237–45.
23. Frantz ID Jr, Dawson EA, Ashman PL, et al. Test of effect of lipid lowering by diet on cardiovascular risk: the Minnesota Coronary Survey. Arteriosclerosis 1989;9:129–35.
24. Dorr AE, Gundersen K, Schneider JC Jr., Spencer TW, Martin WB. Colestipol hydrochloride in hypercholesterolemic patients—effect on serum cholesterol and mortality. J Chronic Dis 1978;31:5–14.
25. Anonymous. The Lipid Research Clinics Coronary Primary Prevention trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984;251:351–64.
26. Anonymous. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate: report from the Committee of Principal Investigators. Br Heart J 1978;40:1069–118.
27. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. JAMA 1982;248:1465–77.
28. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. Stroke 1996;27:373–80.
29. Atkins D, Psaty BM, Koepsell TD, Longstreth WT Jr., Larson EB. Cholesterol reduction and the risk for stroke in men: a meta-analysis of randomized, controlled trials. Ann Intern Med 1993; 119:136–45.
30. Bucher HC, Griffith LE, Guyatt GH. Effect of HMGcoA reductase inhibitors on stroke: a meta-analysis of randomized, controlled trials. Ann Intern Med 1998;128:89–95.
31. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. N Engl J Med 1996;335:1001–9.
32. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.
33. CAPRIE Steering Committee. A randomised, blinded trial of Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE). Lancet 1996;348:1329–39.
34. Tsevat J, Kuntz KM, Orav EJ, Weinstein MC, Sacks FM, Goldman L. Cost-effectiveness of pravastatin therapy for survivors of myocardial infarction with average cholesterol levels. Am Heart J 2001;141:727–34.
35. Stinnett AA, Mittleman MA, Weinstein MC, et al. The cost-effectiveness of dietary and pharmacologic therapy for cholesterol reduction in adults. In: Gold MR, Siegel JE, Russel JE, Weinstein MC, editors. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press, 1996:349–91.
36. Oster G, Huse DM, Lacey MJ, Epstein AM. Cost-effectiveness of ticlopidine in preventing stroke in high-risk patients. Stroke 1994;25: 1149–56.
37. Anderson RN. United States life tables, 1998. National vital statistics reports, vol. 48 no. 18. Hyattsville, MD: National Center for Health Statistics, 2001:9–12.
38. Wright JC, Weinstein MC. Gains in life expectancy from medical interventions—standardizing data on outcomes. N Engl J Med 1998; 339:380–6.
39. Tsevat J, Weinstein MC, Williams LW, Tosteson AN, Goldman L. Expected gains in life expectancy from various coronary heart disease risk factor modifications. Circulation 1991;83:1194–201.