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Cost-Effectiveness of Prescription Recommendations for Cholesterol-Lowering Drugs: A Survey of a Representative Sample of American Cardiologists

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Objectives. **We sought to determine the cost-effectiveness of the recommendations of cardiologists for the pharmacologic treatment of hypercholesterolemia.**

Background. **Despite the publication of guidelines such as the report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, little is known about the national prescribing practices of physicians and how they compare with the recommendations of cost-effectiveness analyses.**

Methods. **Under the auspices of the Cardiovascular Norms Committee of the American College of Cardiology, a nationally representative sample of cardiologists was surveyed, and their recommendations for the pharmacologic treatment of hypercholesterolemia were assessed to determine cost-effectiveness.**

Results. **The 346 responding cardiologists were reasonably representative of the membership of the American College of Cardiology. For the 12 hypothetical patients, the cardiologists recommended pharmacologic treatment more commonly in cases in which previously published studies estimated the treatment to be more cost-effective, although there was a tendency to recommend such treatment for primary prevention even when it was estimated to cost well over $100,000/year of life saved.**

Conclusions. **These findings suggest that the cardiologists' pharmacologic recommendations for lowering lipids are correlated with published cost-effectiveness analyses. However, substantial variation in their recommendations remains, with somewhat less aggressive treatment for secondary prevention and more aggressive treatment for primary prevention than would be recommended on the basis of cost-effectiveness analyses.**

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Since the publication of the first Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (1), several studies (2–6) have examined physicians' compliance with these guidelines. However, the concordance of physicians' practices in the prescription of cholesterol-lowering drugs with published cost-effectiveness analyses of pharmacologic management of hypercholesterolemia (7–14) is less known.

The purpose of this study was to survey the cholesterol-lowering prescription practices of a representative sample of American cardiologists and to assess the cost-effectiveness of these practices. Our data suggest that, at least for the prescription of cholesterol-lowering drugs, cardiologists' practices generally are reasonably consistent with recommendations that would be based on cost-effectiveness considerations.

Methods

The Cardiovascular Norms Committee of the American College of Cardiology was mandated to perform surveys of a representative sample of American cardiologists to learn more about their practice patterns. The number of cardiologists to be surveyed was calculated to ensure that the accuracy of any reported results would be within 5% in either direction of the true rate. The necessary sample size was calculated based on the width of 95% confidence intervals, assuming that 40% of respondents would reply affirmatively, adjusting for sampling from a finite population and increasing the sample size to account for an assumed 60% response rate to the survey. These considerations suggested that 603 (6.3%) of the 9,574 cardiologists comprising the American College of Cardiology should be sampled.

The same proportion (6.3%) of cardiologists was randomly selected in seven geographic regions. Two other regions were slightly oversampled (8.1% and 7.8%) to ensure that at least 33

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cardiologists would be contacted in each region, thus allowing for regional comparisons.

In a 1992 survey this sample of cardiologists was asked to describe their recommendations for diet and drug therapy for 12 hypothetical patients with lipid abnormalities. Cardiologists were informed that the survey was not a test of knowledge, and they were asked to answer questions as they would commonly provide treatment in their primary work setting, assuming that risk factors and contraindications to therapy were absent unless otherwise mentioned. They were to assume that triglyceride levels were measured in the fasting state.

Nonrespondents were sent one reminder letter. Of the 603 cardiologists, 346 (56%) responded and recommended drug treatment with varying frequencies, depending on the case scenario.

These respondents represented the overall membership of the American College of Cardiology in terms of age (mean 48.8 years and 48.5 years, respectively) and gender (male 94.6% and 94.3%, respectively). Based on data from another mailing survey to these 603 cardiologists, the respondents were similar to nonrespondents in terms of work setting and annual number of hours of continuing medical education. Similar proportions of the respondents and nonrespondents performed diagnostic (58% vs. 64%, p = NS) and interventional (39% vs. 43%, p = NS) catheterizations, implanted pacemakers, programmed pacemakers, implanted automatic defibrillators and performed tilt-table testing. Respondents were significantly less likely to perform invasive electrophysiologic testing (6% vs. 13%, $p < 0.01$), but were significantly more likely to perform echocardiograms (86% vs. 75%, $p < 0.01$) or radionuclide procedures (49% vs. 39%, p = 0.05).

Because oversampling and regional differences in prescribing habits were minimal, the prescribing rates reported from this survey were directly calculated as proportions of respondents. No adjustments were made for the weighted sampling scheme.

Members of the Cardiovascular Norms Committee were asked to send questionnaires describing the same 12 case scenarios to two individuals whom they considered to be lipid experts at their own institutions. Responses were received from 18 of these lipid experts. The case scenarios were as follows.

Cases with known coronary heart disease:

Case A. A 53-year old postmenopausal woman experienced stable exertional angina 6 months before being referred to you. Workup revealed diffuse three-vessel coronary artery disease. Her symptoms are easily controlled with medication. She is 15% overweight. Her family history is positive for premature myocardial infarctions. She has been on a restricted diet that stabilized serum lipid levels: total cholesterol 290 mg/dl; low density lipoprotein (LDL) cholesterol 200 mg/dl; high density lipoprotein (HDL) cholesterol 32 mg/dl; triglycerides 290 mg/dl.

Case B. A 50-year old woman had an anterior myocardial infarction during the early morning. She has a 5-year history of diabetes successfully managed with diet and glyburide. Her family history is positive for diabetes and premature myocardial infarctions on her mother's side. She is moderately overweight. She has been on a restricted diet that stabilized serum lipid level: total cholesterol 210 mg/dl; LDL cholesterol 128 mg/dl; HDL cholesterol 30 mg/dl; triglycerides 260 mg/dl.

Case C. A 78-year old man developed nonexertional chest pain. His exercise treadmill test was borderline positive. Coronary arteriography revealed irregular coronary vessel lumen with no lesion >30% reduction diameter. His symptoms have resolved. He has been on a restricted diet that stabilized serum lipid level: total cholesterol 260 mg/dl; LDL cholesterol 190 mg/dl; HDL cholesterol 38 mg/dl; triglycerides 160 mg/dl.

Case D. A 62-year old woman had an anterior myocardial infarction. Her recovery was uneventful. She has been on a restricted diet that stabilized her serum lipid level: total cholesterol 210 mg/dl; LDL cholesterol 125 mg/dl; HDL cholesterol 40 mg/dl; triglycerides 225 mg/dl.

Case E. A 70-year old man underwent coronary artery bypass graft surgery four times for severe diffuse coronary artery disease. He has had two non–Q-wave myocardial infarctions. He stopped smoking 1 year earlier. He has been on a restricted diet that stabilized his serum lipid level: total cholesterol 230 mg/dl; LDL cholesterol 150 mg/dl; HDL cholesterol 35 mg/dl; triglycerides 225 mg/dl.

Case F. A 61-year old man has angina pectoris and severe three-vessel disease, which is deemed inoperable. His family history is positive for coronary artery disease. He has been on a restricted diet that stabilized his serum lipid level: total cholesterol 205 mg/dl; LDL cholesterol 145 mg/dl; HDL cholesterol 38 mg/dl; triglycerides 158 mg/dl.

Case G. A 57-year old man had an inferior wall Q-wave myocardial infarction. His recovery was uneventful. He has been on a restricted diet that stabilized his serum lipid level: total cholesterol 240 mg/dl; LDL cholesterol 160 mg/dl; HDL cholesterol 48 mg/dl; triglycerides 160 mg/dl.

Case H. A 45-year old man experienced the onset of angina at rest. He was adopted and the family history is unknown. He has been on a restricted diet that stabilized his serum lipid level: total cholesterol 820 mg/dl; LDL cholesterol 60 mg/dl; HDL cholesterol 15 mg/dl; triglycerides 4560 mg/dl.

Cases without known coronary heart disease:

Case I. A 44-year old man is referred for evaluation after his 48-year old brother had a myocardial infarction. The family history is positive for premature ischemic heart disease. He has no evidence of coronary artery disease by history, physical examination, electrocardiography or treadmill testing. He presents with serum lipid levels of: total cholesterol 290 mg/dl; LDL cholesterol 220 mg/dl; HDL cholesterol 45 mg/dl; triglycerides 122 mg/dl.

Case J. A 55-year old, mildly obese, diabetic woman is referred for evaluation due to atypical chest pain. Her diabetes has been controlled with insulin for more than 10 years. Cardiac evaluation is normal, including exercise thallium imaging. Her family history is positive for diabetes. She presents with serum lipid levels of: total cholesterol 260 mg/dl; LDL cholesterol 170 mg/dl; HDL cholesterol 35 mg/dl; triglycerides 275 mg/dl.

Case K. A 38-year old man has his cholesterol measured at a business meeting and referred himself for evaluation. He exercises regularly and is in excellent physical condition. His physical examination, electrocardiogram and treadmill test are normal. He presents with serum lipid levels of: total cholesterol 230 mg/dl; LDL cholesterol 155 mg/dl; HDL cholesterol 40 mg/dl; triglycerides 175 mg/dl.

Case L. An asymptomatic 33-year old woman referred herself for evaluation. Her father had a myocardial infarction at age 54. She is in excellent health. She presents with serum lipid levels of: total choles-

terol 234 mg/dl; LDL cholesterol 160 mg/dl; HDL cholesterol 35 mg/dl; triglycerides 195 mg/dl.

Cost-effectiveness calculations. To calculate the cost-effectiveness ratios of the drug therapy recommended by the cardiologists for each of the cases, we used previously published cost-effectiveness analyses of pharmacologic treatment for primary and secondary prevention of coronary artery disease (7,8). Baseline cost-effectiveness ratios, expressed as estimated costs per year of life saved for each case, were derived from an analysis of HMG–coenzyme A reductase inhibition by 20 mg of lovastatin (8). In that report, costs per year of life saved of 20, 40 and 80 mg of lovastatin given every day were tabulated by gender, 10-year age groups and pretreatment cholesterol levels <250 mg/dl or ≥250 mg/dl for secondary prevention. For primary prevention, costs per year of life saved were tabulated by gender, 10-year age groups, pretreatment cholesterol levels of 250 to 299 mg/dl or ≥300 mg/dl and three other risk factors—diastolic blood pressure (<95 mm Hg, 95 to 104 mm Hg and ≥105 mm Hg), current smoking status and percent of ideal weight (<110%, 110% to 129%, ≥130%).

Published cost-effectiveness analyses of cholesterol reduction have not included family history or diabetes as risk factors, so we sought a simplified approach to adjust prior analyses to our case scenarios, because we were interested in the extent to which published data may have affected physicians' practices. Based on our own analysis of the Framingham data and a review of the published reports (15), we estimated that a woman with diabetes would have about the same risk of coronary artery disease as that of a man of the same age and with other similar risk factors; in a man, the increased risk associated with diabetes was considered to be about equal to the risk of smoking as compared with not smoking. The independent relative risk associated with a family history of coronary artery disease is about 1.8 (16–18), which is similar to diabetes, and hence also similar to a man's increased risk associated with smoking.

To estimate the cost-effectiveness ratios for the other drugs chosen by the cardiologists, we multiplied the cost-effectiveness ratios for lovastatin by coefficients derived from the costs per 1% reduction of LDL cholesterol computed by Schulman et al. (7) in their clinical model: costs per 1% reduction of LDL cholesterol were $139 for niacin, $177 for 20 mg of lovastatin, $289.90 for gemfibrozil, $334.54 for probucol and $347 for cholestyramine. The coefficients we calculated were the ratios of the cost per 1% reduction of LDL cholesterol for drug divided by the cost per 1% reduction of LDL cholesterol for 20 mg of lovastatin given every day. The resulting coefficients were 0.785 for niacin ($139/$177), 1.64 for gemfibrozil ($289.90/$177), 1.89 for probucol ($334.54/$177) and 1.96 for cholestyramine ($347/$177). To the extent to which increasing doses of lovastatin and other medications cost relatively more per percent reduction in LDL cholesterol, all of the calculated cost-effectiveness ratios were somewhat more favorable than if patients were put on high dose medication to lower cholesterol very aggressively. However, because all but one case had moderate hypercholesterolemia, at most, this approach to calculating cost-effectiveness was believed to be preferable to arbitrary assumptions about all patients being titrated to some specific cholesterol level.

Finally, to summarize physician preferences for one drug over another, the median cost-effectiveness ratio for drug therapy for each case scenario was calculated. For example, for a given case, if the cost-effectiveness ratio of 20 mg of lovastatin was $1,000 per year of life saved and 20% of the cardiologists who decided that drug therapy was indicated prescribed lovastatin, 20% prescribed gemfibrozil and 60% niacin, the median cost-effectiveness ratio of the cardiologists' drug therapy for that case would have been $1,000 × 0.785, or $785 per year of life saved. Note that this analysis calculates the median marginal cost-effectiveness of drug therapy for each case; physicians who did not recommend medications for a specific case do not contribute to the calculation. The use of median values reduced the influence of occasional physicians who might choose very expensive drugs; analyses using the mean of the individual cost-effectiveness ratios of each physician gave qualitatively similar results. Median cost-effectiveness ratios of the drug therapy recommended by the lipid experts were calculated similarly as for drug therapy recommended by cardiologists.

We computed the cost-effectiveness ratios in dollars per year of life saved for the pharmacologic therapy recommended for each case of primary and secondary prevention, with the exception of Case C, whose description was misleading to many cardiologists and made it impossible for them to classify the case in a primary or a secondary prevention model.

Statistical analysis. Comparisons between cardiologists and lipid experts were performed using the Wilcoxon test for cost-effectiveness ratios and the Fisher exact test for the proportions of respondents who would prescribe medications. Because of the multiple comparisons being examined, statistical significance was defined as $p < 0.01$.

Ninety-five percent confidence intervals were computed for median cost-effectiveness ratios using a multistep simulation process. First, the usual 95% confidence intervals were calculated for the proportions of cardiologists prescribing each medication. Then, a proportion was generated at random from within each confidence interval, with the restriction that the proportions summed to 1. Finally, these simulated proportions were used to generate new, "simulated" decisions from each of the participating cardiologists. A simulated median cost-effectiveness ratio was calculated based on these decisions. This simulation was repeated 1,000 times, and 95% confidence intervals were taken from the appropriate extremes of these 1,000 replications. Because only five medications were considered, the median cost could only take on one of five possible values. Therefore, in most cases, the estimated median will be found to be very stable in the sense that the upper and lower confidence limits will be exactly equal to the estimated median.

Results

The clinical characteristics, risk factor profile and total cholesterol levels for secondary prevention cases (A through

Table 1. Clinical Characteristics and Risk Factors of Primary and Secondary Prevention Cases

Case	Age (yr)/ Gender	Total Cholesterol (mg/dl)	Risk Factors				
			Smoking	Hypertension	Obesity	Diabetes	Family History of CAD
Primary Prevention							
A	53/F	290	–	–	+	–	+
B	50/F	210	–	–	+	+	+
D	62/F	210	–	–	–	–	–
E	70/M	230	+	–	–	–	–
F	61/M	205	–	–	–	–	+
G	57/M	240	–	–	–	–	–
H	45/M	820	–	–	–	–	–
Secondary Prevention							
I	44/M	290	–	–	–	–	+
J	55/F	260	–	–	+	+	–
K	38/M	230	–	–	–	–	–
L	33/F	234	–	–	–	–	+

CAD = coronary artery disease; – = negative; + = positive.

H) and primary prevention cases (I through L) are summarized in Table 1. The proportion of cardiologists who recommended various forms of medications varied widely from case to case (Table 2), with lovastatin usually the most popular medication for both primary and secondary prevention. The median cost-effectiveness ratios of the cardiologists' drug therapy recommendation for each of the secondary prevention cases (A through H) was $36,000 or less per year of life saved. For primary prevention cases (I through L), costs per year of life saved for recommended pharmacologic treatment were much less favorable, even for case J with two risk factors, because of her female gender.

The median cost-effectiveness ratios of cardiologists' drug therapy recommendations for secondary prevention cases and primary prevention cases (Fig. 1) showed a clear inverse relation between the cost per year of life saved of a pharmacologic treatment and the percentage of cardiologists who chose it. Fewer cardiologists considered drug treatment for primary prevention than for secondary prevention, and the percentage of cardiologists who thought that drug treatment was appropriate for the most expensive secondary prevention case (case D) was 24%, whereas the highest percentage of cardiologists who considered drug treatment for a primary prevention case was 31% (case I).

The lipid experts' responses were generally similar to those of the cardiologists. Although a larger percentage of lipid experts recommended drug treatment for cases D and F ($p < 0.01$), the cost-effectiveness ratios of the recommended treatment strategies for these two cases were not significantly different for the cardiologists compared with the lipid experts. The cost-effectiveness ratios for cases A and J were significantly lower for lipid experts than for cardiologists because the

Table 2. Choices of Pharmacologic Therapy

Case	Medication					% Prescribing Medications	Median Costs/Year of Life Saved*
	Niacin	Lovastatin	Cholestyramine	Gemfibrozil	Other		
A	47 (14%)	165 (48%)	23 (7%)	90 (27%)	3 (0.9%)	97	$ 3,500
B	25 (7%)	14 (4%)	7 (2%)	129 (37%)	3 (0.9%)	51	$ 26,000
D	25 (7%)	18 (5%)	9 (3%)	26 (8%)	2 (0.6%)	24	$ 36,000
E	43 (13%)	105 (31%)	20 (6%)	67 (20%)	1 (0.3%)	70	$ 25,000
F	32 (10%)	130 (38%)	22 (6%)	17 (5%)	1 (0.3%)	59	$ 17,000
G	24 (7%)	149 (45%)	46 (14%)	10 (3%)	0	69	$ 17,000
H	35 (11%)	74 (22%)	15 (5%)	164 (49%)	9 (3%)	90	Negative or minimal costs
I	11 (3%)	71 (21%)	19 (6%)	1 (0.3%)	0	31	$ 370,000
J	10 (3%)	26 (8%)	11 (3%)	50 (14%)	2 (0.6%)	29	$ 121,000
K	1 (0.3%)	3 (0.9%)	0	1 (0.3%)	1 (0.3%)	1.5	$ 690,000
L	0	1 (0.3%)	1 (0.3%)	2 (0.6%)	0	1.2	> $1,000,000

*Simulated 95% confidence limits show that these estimates of median costs are stable (i.e., upper limit equals lower limit equals reported median) for all but case D, where the cost could be as high as $59,000; case J, where cost could be as low as $74,000; and case K, where cost could be as low as $542,000 or as high as >$1,000,000. Confidence limits are not provided for cases H and L, where exact cost-effectiveness ratios are not presented.

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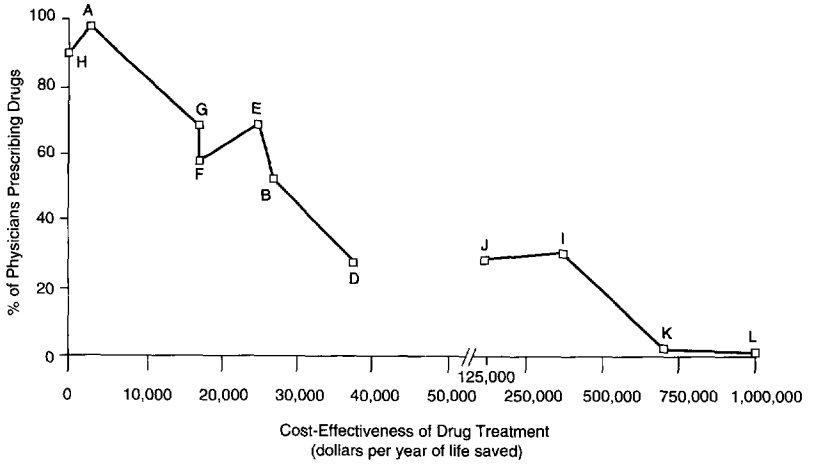

Figure 1. Relation between the cost-effectiveness of drug treatment and the percentage of cardiologists who recommended drugs. **Letters** refer to individual cases. See Methods for details.

lipid experts were more likely to prescribe niacin rather than lovastatin.

Discussion

In January 1988, the NCEP (1) guidelines were published. This step by the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults was the logical consequence of epidemiologic studies showing that total cholesterol and LDL cholesterol levels were independently associated with coronary artery disease rates and of randomized clinical trials that revealed a decrease in the incidence of coronary events in middle-aged men with high blood cholesterol who were assigned to cholesterol-lowering drugs.

Physician practice patterns. These guidelines increased the percentage of physicians who considered total cholesterol a risk factor from 39% in 1983 to 99% in 1990 (2), and physicians reported treating serum cholesterol levels at lower levels in 1990 than in 1986 or 1983. Although more diversity remained among physicians in treating hypercholesterolemia than in treating hypertension, the evolution of physicians' practices in the early years of the NCEP was considered similar or even faster for hypercholesterolemia than for hypertension in the early years of the National High Blood Pressure Education Program (3).

However, the results of other studies were less optimistic. In 1988, compliance with the NCEP recommendations for documenting desirable total cholesterol values or appropriately responding to abnormal values among residents at the Metrohealth Medical Center, Cleveland, Ohio, averaged 39% (4), and residents markedly overestimated their own compliance. In 1989 and 1990, 24% of physicians in Wisconsin still did not recognize 240 mg/dl as an elevated cholesterol level nor did they treat hypercholesterolemia in line with the recommendations (5); no differences were observed among specialty groups. Interestingly, although dietary counselling for hypercholesterolemia was common among primary care physicians (6), low rates were observed for starting cholesterol-lowering medications. Less dogmatic NCEP guidelines for drug therapy than for dietary therapy, as well as the lack of unanimity in the medical community about drug treatment for hypercholesterolemia, were considered as possible explanations.

Cost-effectiveness. In an era of concern about health care costs, it would have been surprising if the issue of the cost of pharmacologic treatment for hypercholesterolemia, highlighted by specific cost-effectiveness analyses (7–13,19), did not affect the drug prescribing patterns of American physicians. The results of our study are consistent with this hypothesis and show a clear inverse relation between the cost-effectiveness of drug therapy and the percentage of cardiologists who would consider it. The costs per year of life saved reported in our results reflect the fact that, for secondary prevention, drug therapy is effective (20) and generally has favorable cost-effectiveness ratios. For primary prevention, cost-effectiveness ratios of drug therapy are favorable only in selected high risk subgroups (7–13,19).

The fact that an inverse relation between cost-effectiveness ratios and the percentage of cardiologists who considered drug therapy existed not only for primary prevention but also for secondary prevention, where cost-effectiveness ratios were more favorable overall, highlights physicians' current concern about the cost of their prescribing practices. A previous study (21) reported that physicians at a university hospital considered that costs had an important influence on their prescribing behavior, even if most of them, when presented with specific situations, were unaware of the actual prices of the medications they prescribed and seemed more influenced by what was routinely prescribed by others than by costs. Similarly, information on costs, as well as on clinical and pharmacologic issues, were shown to improve physicians' prescribing habits in another study (22). Our results also suggest that published analyses on the cost-effectiveness of drug therapy may influence practice patterns more so than trials of more aggressive interventions such as thrombolysis (23,24), as has been noted in the results of randomized clinical trials of cardiovascular drugs after acute myocardial infarction (25).

A limitation of our study is that the two prior studies (7,8) from which we derived our cost-effectiveness ratios did not

consider any effects of cholesterol reduction on noncoronary death rates. Although meta-analyses of primary prevention trials (26–29) and analyses of low risk groups in both primary and secondary prevention trials (30,31) revealed higher rates of noncardiovascular deaths in men receiving cholesterol-lowering drugs, the largest secondary prevention trial found no increase in noncardiovascular deaths (20). Even if cost-effectiveness ratios for this study were recalculated to consider possible noncoronary adverse effects, the inverse relation observed between the cost-effectiveness ratios of drug treatment and the percentage of physicians who would consider it would persist.

Conclusions. Despite the consistent trend toward decreasing prescription use in patients with lower cost-effectiveness ratios, the thresholds for prescribing cholesterol-lowering drugs varied among cardiologists. Only ~60% of cardiologists would prescribe drugs in secondary prevention cases in which the cost-effectiveness ratio was favorable, and ~30% would prescribe medications in primary prevention cases in which the ratio was estimated to be unfavorable. These findings in the "middle range" cases emphasize the need for more research to determine whether the estimated cost-effectiveness ratios are truly accurate and whether improved education programs influence practice based on the best available data. The effects of such research on prescription practices, as well as of the Second Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II) (32), will have to be evaluated.

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