

How Effective Is Drug Treatment Of Hypercholesterolemia? A Guided Tour Of The Major Clinical Trials For The Primary Care Physician

Kevin Grumbach, M.D.

Abstract: Background: Drug treatment of hypercholesterolemia remains controversial. Central to the debate are the results of the major placebo-controlled clinical trials of pharmacologic treatment of hypercholesterolemia.

Methods: Conventions and principles of clinical epidemiology are used to review the four major clinical trials of drug treatment of hypercholesterolemia. The review translates the results of these large, epidemiologically oriented experiments into terms that are applicable to managing patients at the individual level.

Results: Clofibrate is an ineffective treatment. Primary prevention with gemfibrozil or cholestyramine requires treating approximately 50 middle-aged men for 10 years to avert one adverse outcome. Secondary prevention with niacin for men with a prior myocardial infarction requires treatment of 10 to 15 patients for 10 years to prevent one adverse outcome.

Conclusions: While drug treatment of hypercholesterolemia in middle-aged men can prevent death and morbidity, the magnitude of the effectiveness is modest. Because a critical factor influencing the magnitude of benefit is the underlying risk of adverse events in the population under treatment, physicians should target interventions to populations that may benefit the most. In populations for whom the magnitude of effectiveness is likely to be modest, physicians should exercise clinical judgment when deciding what degree of benefit justifies treatment in individual cases. (J Am Board Fam Pract 1991; 4:437-45.)

Drug treatment of hypercholesterolemia remains controversial. While many assume that the National Cholesterol Education Program Panel treatment guidelines¹ define the standard of care for hypercholesterolemia, reports in both the professional and lay literature have challenged these guidelines as being overly aggressive in recommending pharmacologic interventions.²⁻⁸ Adding to the confusion, advocates of either aggressive or conservative practices frequently invoke the results of the same clinical trials to defend widely disparate points of view.

What accounts for the disagreement over treatment of hypercholesterolemia? Do the results of the major clinical trials conflict? Are the facts in

dispute, or is the debate over issues of interpretation and clinical judgment? Is it possible to quantify objectively the benefits and risks of drug treatment? Are the results of controlled research trials applicable to the real world of clinical practice?

Insights into the answers to these questions can result from examining the major clinical trials that constitute much of the empirical basis for hypercholesterolemia treatment guidelines. Part of the challenge in examining these trials, however, is translating the results of large, epidemiologically oriented experiments into terms applicable to caring for patients at the individual level. This article discusses the principles and conventions of clinical epidemiology that facilitate this translation and then uses these principles to evaluate the major trials of drug treatment of hypercholesterolemia.

Clinical Trials in Perspective

Large, population-based studies, such as the Framingham project, have established that persons

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From the Department of Family and Community Medicine and the Institute for Health Policy Studies, University of California, San Francisco. Dr. Grumbach was a Pew Health Policy Fellow at the time this article was written. Address reprint requests to Kevin Grumbach, M.D., San Francisco General Hospital, Bldg. 1, Room 202, 1001 Potrero Avenue, San Francisco, CA 94110.

Table 1. Relative and Absolute Risk Reduction: Hypothetical Examples.

Example	Adverse Events*	Percent Relative Risk Reduction†	Absolute Risk Reduction*‡
1. Placebo	40	75	30
Drug	10		
2. Placebo	4	75	3
Drug	1		
3. Placebo	14	21	3
Drug	11		

*per 100 subjects.

†Relative risk reduction = $[(\text{Rate}_{\text{placebo}} - \text{Rate}_{\text{Rx}}) / \text{Rate}_{\text{placebo}}] \times 100\%$.

‡Absolute risk reduction = $\text{Rate}_{\text{placebo}} - \text{Rate}_{\text{Rx}}$.

with hypercholesterolemia have a significantly increased probability of developing cardiovascular disease and of dying at a younger age than those with lower cholesterol levels.^{9,10*} In addition, many short-term studies have shown that pharmacologic treatment can reduce cholesterol levels to a normal range in persons with elevated levels. Why, in the face of these two bodies of evidence, is it necessary to perform long-term trials costing millions of dollars to evaluate drug treatment? If persons with lower cholesterol levels are at lower risk of disease, and if drugs reduce cholesterol levels, is it not reasonable to assume that drug treatment will reduce the incidence of disease?

There are a number of reasons to exercise caution in making this assumption. Having normal levels of cholesterol may not be the same as having levels normalized by drug treatment. Although associated with a higher risk of cardiovascular disease, hypercholesterolemia may not be the actual *cause* of disease. For example, cholesterol simply might be a marker for some unidentified dietary or physiologic factor that is the true instigator of atherosclerosis, and reducing serum cholesterol levels with drug treatment might not correct the underlying process. In addition, drug treatment might produce side effects that partly or completely offset the gains achieved by risk factor reduction. For these reasons, among others, it is important to perform trials that carefully measure the actual clinical outcomes of drug intervention.

*Although there is general agreement that hypercholesterolemia is a risk factor for cardiovascular disease and overall mortality in middle-aged men, whether hypercholesterolemia raises the risk in older men and in women of any age is not entirely clear.^{4,10}

Treatment Effectiveness

A preventive intervention is effective if it is able to reduce the occurrence of adverse clinical outcomes. One way to express effectiveness is as the proportion of adverse events averted by treatment—the *relative risk reduction*. Alternatively, one can formulate effectiveness as the actual number of adverse events prevented by treatment, or the *absolute risk reduction*.¹¹

Table 1 illustrates the different information communicated when effectiveness is expressed as either relative risk reduction or absolute risk reduction. In example 1, 40 of 100 untreated patients experienced an adverse outcome compared with only 10 of 100 treated patients. Treatment thus prevented 75 percent $[(40-10)/40]$ of the events, representing the relative risk reduction. In absolute terms, treatment of 100 patients prevented 30 untoward outcomes—the absolute risk reduction. In the second example, only 4 of 100 untreated patients had adverse events while 1 of 100 treated patients had such an event. The relative risk reduction is 75 percent, the same as in example 1; however, the absolute risk reduction is only 3 events averted per 100 patients treated compared with 30 per 100 in example 1.

Examples 1 and 2 highlight one of the basic challenges facing primary care physicians attempting to interpret the results of clinical trials. Investigators tend to emphasize effectiveness in terms of relative risk reduction, while clinicians tend to be more interested in knowing how many of the patients they treat will actually benefit (the absolute risk reduction).^{2,11} As shown in Table 1, treatment of the same relative effectiveness may produce a tenfold difference in absolute effectiveness, depending on the underlying rate of adverse events in the untreated population.

Example 3 in Table 1 shows how a treatment of less relative effectiveness than the treatment in example 2 could still yield an absolute risk reduction of 3 per 100 simply by treating a population with a higher underlying risk of adverse outcomes (14 per 100 as opposed to 4 per 100).

Relative risk reduction is primarily a function of the intrinsic efficacy of the intervention (how well the drug itself works), compliance with the drug (how faithfully the patient takes the drug), and the proportion of adverse outcomes caused by the risk factor in the first place (the attributable risk). Attributable risk limits the ultimate effec-

tiveness of treatment for a multifactorial disease, such as coronary artery disease, because even the best cholesterol-reducing medication will not entirely avert progression of coronary disease that is due to, for example, continued smoking.

Absolute effectiveness is a product of both the relative risk reduction and the underlying rate of adverse events. As example 2 in Table 1 shows, even a treatment that is highly efficacious in relative terms may yield modest benefit if the underlying incidence rate is low. In other words, even the best medication is of limited benefit if few people are going to experience bad events even without treatment. Absolute risk reduction best reflects the primary care physician's vantage point in relating the number of patients benefiting to the number actually started on treatment.

Laupacis and colleagues¹¹ have proposed an even simpler formulation of absolute risk reduction, which they refer to as the *number of patients needed to treat* to avert one adverse outcome. The number needed to treat is simply the reciprocal of the absolute risk reduction. In example 1 of Table 1, the absolute risk reduction of 30 events prevented for every 100 patients treated may be reformulated as needing to treat approximately 3 (100/30) patients to avert one event.

For each of the studies in this review, the figures for relative risk reduction, absolute risk reduction, and number needed to be treated are provided.

Clinical Outcomes

If effectiveness defines a treatment's success at preventing adverse outcomes, what are the clinical outcomes that merit consideration? Obviously, investigators conducting hypercholesterolemia treatment trials are particularly interested in measuring cardiovascular outcomes, such as myocardial infarctions and strokes. Published reports typically highlight reductions in cardiovascular deaths, nonfatal cardiovascular events, and total cardiovascular events.

Primary care physicians, not to mention patients, may have a slightly broader perspective on meaningful clinical outcomes. The ultimate question—Did patients receiving active treatment live longer?—tends to be more relevant than knowing only about deaths from a particular cause. Similarly, many of us are interested in knowing how

the overall quality of life fared among treated and control subjects, not exclusively about cardiovascular morbidity.

Considering all clinically meaningful outcomes is important, because in several of the trials reviewed here, reductions in cardiovascular deaths are offset by increases in noncardiovascular deaths. Clinical trials of risk factor interventions, often requiring thousands of patients and many years of treatment to show measurable benefit, may detect toxicities that were not apparent in the more limited studies required for initial drug licensing.

In presenting the results of the major clinical trials, this review focuses on the outcomes of (1) death from any cause, (2) cardiovascular morbidity (nonfatal myocardial infarctions), and (3) combined all-cause mortality and cardiovascular morbidity. Also highlighted are reports showing significant differences in noncardiovascular morbidity between treated and control groups.

Review of the Major Clinical Trials

Selection Criteria

In selecting published trials for this review, only those studies adhering to a relatively rigorous definition of the classic randomized, placebo-controlled clinical trial—the “gold standard” of experimental design—were chosen. The selection criteria were as follows:

1. The study included a pharmacologic intervention for hypercholesterolemia, rather than dietary treatment alone.
2. The study randomized assignment of subjects to treatment and control groups.
3. The study compared active treatment with placebo treatment.
4. The primary outcomes were death and clinically apparent disease, rather than less-overt outcomes, such as the status of coronary atherosclerosis viewed by angiogram.¹²

Hypercholesterolemia Trials

Tables 2 and 3 summarize the four major hypercholesterolemia treatment trials.¹³⁻¹⁶ The World Health Organization (WHO), Lipid Research Clinics (LRC), and Helsinki Heart studies all examined primary prevention, i.e., treatment of subjects with no overt manifestations of cardiovascular disease. The Coronary Drug

Table 2. Hypercholesterolemia Trials—Study Characteristics.*

Study	Subjects	Initial Cholesterol Level	Drug
WHO ¹³	Men only 30–59 years old No overt cardiovascular disease	Average = 6.45 mmol/L (250 mg/dL) (top 33% of sampled population)	Clofibrate
LRC ¹⁴	Men only 33–59 years old No overt cardiovascular disease No hypertension	Average = 7.55 mmol/L (292 mg/dL) (top 5% of sampled population) Average LDL = 5.53 mmol/L (216 mg/dL)	Cholestyramine
Helsinki ¹⁵	Men only 40–55 years old No overt cardiovascular disease	Average = 7.00 mmol/L (270 mg/dL) (top 20% of sampled population) Average LDL = 4.86 mmol/L (190 mg/dL)	Gemfibrozil
CDP ¹⁶	Men only 30–60 years old 1 or more prior myocardial infarctions	Average = 6.45 mmol/L (250 mg/dL) (not selected for high cholesterol)	Clofibrate or niacin

Project (CDP) studied secondary prevention in subjects with a history of myocardial infarction. All of the trials examined middle-aged men exclusively.

The three primary prevention trials selected men with elevated total cholesterol levels using criteria ranging from the upper 33 percent of screened values in the WHO study to the upper 5 percent of values in the LRC study. The CDP trial of secondary prevention selected men with a prior myocardial infarction irrespective

of their cholesterol level, although the average cholesterol level was relatively high (6.45 mmol/L [250 mg/dL]).

Drug treatments included clofibrate, niacin, cholestyramine, and gemfibrozil. No major study of clinical outcomes has been reported with lovastatin or oat bran. Subjects both on active drug and placebo treatment received dietary counseling. In all studies, cholesterol levels declined to a significantly greater degree in subjects on active treatment.

Table 3. Hypercholesterolemia Trials—Clinical Outcomes.

Study	Years of Follow-up	Outcomes	Incidence*		Relative Risk Reduction (%)	Absolute Risk Reduction*	Number Needed To Treat†
			Placebo	Drug			
WHO ¹³	5	Death	19	25	-24	-6	-167
		Nonfatal MI	31	23	26	8	125
		Death or nonfatal MI	50	48	NS		
LRC ¹⁴	7.4	Death	37	36	NS		
		Nonfatal MI	118	102	14	16	63
		Death or nonfatal MI	149	135	9	14	71
Helsinki ¹⁵	5	Death	21	22	NS		
		Nonfatal MI	35	22	37	13	77
		Death or nonfatal MI	56	44	20	12	83
CDP ¹⁶	6.2	Niacin group					
		Death	254	244	NS		
		Nonfatal MI	138	102	26	36	28
	Death or nonfatal MI	392	346	12	46	22	
	15‡	Death	582	520	11	62	16
	Clofibrate group	6.2	Death	254	255	NS	
Nonfatal MI			138	131	NS		
Death			582	578	NS		

MI = myocardial infarction. NS = no statistically significant difference between placebo and drug groups.

*Incidence and absolute risk reductions expressed as events per thousand subjects.

†Number of subjects needed to be treated to avoid one event.

‡15-year follow-up study conducted after completion of treatment phase (only overall mortality measured).

As indicated in Table 3, not one of the studies showed a significant reduction in overall mortality among subjects on active drugs during the study period. In the WHO study, overall mortality was significantly higher among subjects taking clofibrate because of an excess of noncardiovascular deaths. In the LRC (cholestyramine) and Helsinki (gemfibrozil) studies, small decreases in cardiovascular mortality were counterbalanced by small increases in noncardiovascular mortality.

In terms of nonfatal outcomes, all four studies consistently showed a benefit of treatment in preventing nonfatal myocardial infarctions. The number needed to treat to avert one nonfatal myocardial infarction ranged from 28 patients for 6.2 years in the CDP-niacin group to 125 patients for 5 years in the WHO study. Treatment had no impact on the incidence of stroke and peripheral vascular disease.

In addition to its uniqueness as a trial of secondary prevention, the CDP study had a follow-up component that distinguishes it from the other studies.¹⁷ Several years after the CDP trial was formally concluded, investigators attempted to determine whether there were any long-term or delayed effects of treatment on overall mortality. At the 15-year follow-up, overall mortality was significantly lower among subjects who had received niacin while they were enrolled in the trial. Unfortunately, the CDP follow-up study included no information about

nonfatal outcomes, type of ongoing medical and pharmacologic treatment, or health behavior for the years between the conclusion of the formal trial and the follow-up ascertainment of vital status. It is difficult therefore to be certain whether the diverging death rates represent delayed direct effects of niacin treatment, indirect effects of the initially lower nonfatal myocardial infarction rate translating into lower mortality with time, or the effects of unspecified treatments and behaviors in the intervening years.

To allow direct comparison of the effectiveness of treatment among the hypercholesterolemia trials, the results were extrapolated to a uniform 10-year duration of treatment for all the studies (using the methods of Laupacis, et al.¹¹). These 10-year "numbers needed to treat" to prevent either death or a nonfatal cardiovascular event are shown in Figure 1. These projections should be regarded as estimates of the general magnitude of benefit of treatment in the various studies.

Side Effects of Treatment

Table 4 presents many of the symptoms or clinical conditions reported to occur more frequently in subjects on active drug in the hypercholesterolemia trials. The format follows that of the morbidity and mortality tables, but with headings of relative risk and absolute risk (rather than risk reduction). Number needed to treat refers to the

Table 4. Treatment Side Effects.

Study	Rx Group	Outcomes	Incidence*		Relative Risk	Absolute Risk*	Number Needed to Treat†
			Placebo	Drug			
WHO ¹³	Clofibrate	Cholecystectomy	5	11	2.2	6	167
CDP ¹⁶	Clofibrate	Cholelithiasis	13	30	2.3	17	59
		Impotence or decreased libido	100	141	1.4	41	24
		Niacin	Gout	43	64	1.5	21
	Niacin	Flushing	43	920	21.4	877	1
		Skin abnormalities	158	263	1.7	105	10
		Abdominal pain	143	214	1.5	71	14
Helsinki ¹⁵	Gemfibrozil	"Moderate to severe upper gastrointestinal symptoms" (1st year)	70	113	1.6	43	23
LRC ¹⁴	Cholestyramine	"Moderate to severe gastrointestinal side effects" (1st year)	430	680	1.6	250	4

*Incidence and absolute risk expressed as events per thousand subjects.

†Number of subjects needed to be treated to produce one side effect.

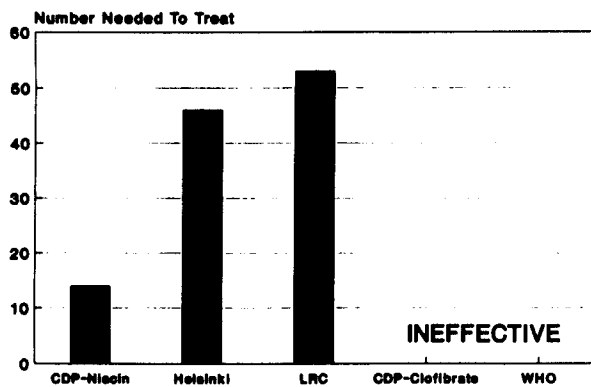


Figure 1. Number of patients needed to be treated for 10 years to avert 1 adverse event. (CDP-Niacin = Coronary Drug Project, niacin group; Helsinki = Helsinki Heart trial [gemfibrozil]; LRC = Lipid Research Clinics trial [cholestyramine]; CDP-Clofibrate = Coronary Drug Project, clofibrate group; WHO = World Health Organization trial [clofibrate].)

number of patients receiving treatment that is expected to result in one adverse side effect occurring. Side effects range from mild and reversible, but extremely common, occurrences (e.g., flushing with niacin) to more severe but less frequent conditions (e.g., cholelithiasis with clofibrate).

Discussion

Targeting Subpopulations at Highest Risk

What accounts for the superior absolute effectiveness of treatment with niacin in the CDP study? As Table 3 indicates, this result is not due to a greater relative risk reduction in the niacin-CDP study. For the outcome “death or cardiovascular morbidity,” the 12 percent relative risk reduction in the niacin-CDP group was comparable with the 9 percent relative risk reduction in the LRC trial; both were considerably less than the 20 percent relative risk reduction in the Helsinki study. The key factor explaining the difference in absolute risk reduction is the much higher underlying rate of adverse events in the CDP study. The underlying event rate in the CDP placebo group (392 of 1000) was nearly three times the rate in the LRC placebo group (149 of 1000) and six times the rate in the Helsinki placebo group (56 of 1000). Clearly, subjects in the CDP trial were different. They had already suffered a myocardial infarction, placing them at much higher risk of death or subsequent infarction, even though their average cholesterol level was less than that of

subjects in the Helsinki study. The magnitude of this difference in underlying event rate far outweighs differences in factors influencing relative risk reduction (e.g., the different efficacies of particular drugs) in determining the absolute effectiveness in these studies. On the other hand, the lack of any relative risk reduction with clofibrate in both the WHO and CDP studies indicates that clofibrate is an inherently ineffective drug (e.g., with no benefit or with risk exceeding benefit) no matter what the underlying event rate.

The difference in the magnitude of effectiveness between the niacin-CDP study of secondary prevention and the three primary prevention hypercholesterolemia trials shows one of the great ironies of preventive medicine: secondary prevention is often more effective than primary prevention in terms of the magnitude of absolute risk reduction because it targets a subpopulation that has declared itself to be at particularly high risk of future events. Saying that secondary prevention is more effective than primary prevention may sound heretical. Indeed, preventing a second myocardial infarction may be a lesser accomplishment than preventing the first infarction. My point is not to discredit the laudable goal of primary prevention; nevertheless, primary prevention invariably increases the number needed to treat to prevent an event because many persons are treated who were never destined to experience cardiovascular disease.

In the best of all possible worlds, clinicians could predict exactly which patients will develop cardiovascular disease and limit risk factor interventions to those individuals. Because currently available measures to define risk, such as blood pressure or cholesterol levels, are often at best rough predictors of adverse clinical outcomes, clinicians face treating risk factors in many patients who would have done equally well (or better) without treatment. As these clinical trials indicate, treating risk factors in populations with low underlying rates of adverse events leads to large numbers of patients needing to be treated to avert a single event. This will be the case with the best of medications, i.e., one producing a high relative risk reduction. For primary care physicians, then, selecting the population of patients to target for treatment becomes as important as or even more important than selecting the particular drug for treatment.

The recommendations of the National Cholesterol Education Project (NCEP)¹ attempt to target subpopulations at particular risk by including risk factors other than just hypercholesterolemia into many of the treatment algorithms for hypercholesterolemia. It should be noted, however, that subjects in the hypercholesterolemia trials had many of the additional risk factors featured in the NCEP guidelines: all were men, and some smoked, had family histories of premature cardiovascular disease, and so on. The numbers needed to treat listed in Figure 1 may be reasonable estimates of the effectiveness of treating the types of populations targeted by the NCEP guidelines.

How Effective Should a Treatment Be?

Brett,² in a commentary on hypercholesterolemia, describes drug treatment of cardiovascular risk factors as “an enterprise in probabilities that incorporates scientific data, the patient’s values, and the patient’s attitude toward medical interventions while asymptomatic.”^{p 679} The results of the major clinical trials of drug treatment of hypercholesterolemia provide some of the best scientific data about treatment effectiveness. In the case of severe hypertension, a risk factor for which studies have shown that the number needed to treat to avert a death or morbid cardiovascular event is only 5 patients for 1.5 years,¹⁸ the scientific data may be so compelling as to eliminate all controversy about the merits of treatment. But in instances when effectiveness appears more modest, questions of values assume greater prominence. A critical factor in treatment decisions becomes the primary care physician’s judgment about what level of effectiveness justifies treatment in individual cases.

How should a physician and a patient decide whether effectiveness in the range of a 1-in-50 chance of benefiting from treatment of hypercholesterolemia is worth it? The choice to intervene may be straightforward when a preventive intervention, such as a vaccine, is cheap, relatively nontoxic, and minimally disruptive to patients’ lives. Unfortunately, long-term drug treatment of risk factors is considerably more complicated when evaluating the tradeoffs of intervention.

Patients and physicians must weigh the possible compromises in quality of life that may accompany the potential benefits of taking medication.

While some persons are eager to “do everything possible” to prevent disease and willingly accept the tradeoffs of long-term medication, others are less favorably inclined to medical intervention. As Table 4 shows, drug side effects are relatively common with many of the agents. Patients clearly will differ in their attitudes about tolerating some immediate and potentially self-limited discomfort for the chance of averting some major mishap in the future. There is evidence that the act of detecting hypertension and labeling an individual as hypertensive may result in deteriorating psychological well-being and increased work absenteeism.^{19,20} Patients also have different views about the “medicalization” of their lifestyles entailed by the use of medications and the frequent visits and laboratory tests that accompany treatment. Medicalization is particularly important when the population considered for treatment is asymptomatic. As Brett and others note,²²¹ drug side effects and issues of medicalization make *taking* a medication very different from *giving up* fatty foods or cigarettes.

These considerations should be part of every physician-patient deliberation, no matter what the diagnosis or treatment.²² But they take on increasing importance when an intervention offers a 1-in-50 chance of benefit rather than a 1-in-5 chance. Among both physicians and patients, disagreements about the overall balance of risk and benefit are inevitable when the magnitude of treatment effectiveness is modest.

Examining magnitudes of effectiveness can also help physicians to prioritize their clinical activities. How can a physician make best use of the 10 to 15 minutes spent with a patient during an office visit? In general, clinical trials suggest that treating mild to moderate hypertension is more effective than treating hypercholesterolemia in asymptomatic individuals.²³⁻²⁵ Facing a patient with both hypertension and hypercholesterolemia, a physician might want to emphasize reducing blood pressure—for example, by prioritizing antihypertensive medication if the patient experiences difficulty tolerating both antihypertensive and cholesterol-lowering medications. Counseling a patient to quit smoking probably has greater benefit than drug treatment of either mild to moderate hypertension or hypercholesterolemia.²⁶ Even so, more than one-half of the smokers who visited a physician

in the previous year state their physician never advised them to quit smoking.²⁷ To the extent that preoccupation with interventions for hypercholesterolemia distracts physicians from counseling patients to discontinue smoking, physician resources are inefficiently used.

It is instructive to compare American consensus reports with those of other countries. Partly on the basis of the same clinical trials reviewed herein, one British panel has rejected mass cholesterol screening²⁸ and other British panels have been much more cautious in advising drug treatment of hypercholesterolemia.^{29,30} A Scottish authority has suggested that drug treatment of hypercholesterolemia be reserved for secondary prevention.³¹ Some Canadian guidelines for drug treatment of hypercholesterolemia have also been less vigorous than the guidelines of the American NCEP.³² Physicians should keep in mind the broader cultural and economic values that influence the thresholds of effectiveness considered reasonable for adopting interventions on a wide scale into clinical practice.³³

Conclusion

Whether as a member of an expert panel developing practice guidelines, as a participant in a peer-review committee for a teaching program or group practice, or as a practitioner developing individualized patient care plans, physicians must rely on the results of clinical research to make well-informed decisions about the appropriateness of clinical interventions. The following principles incorporated into this review of hypercholesterolemia are equally applicable to the analysis of other clinical topics:

1. Focus on the absolute as well as relative risk reduction.
2. Scrutinize the inclusiveness and clinical relevance of the outcomes measured.
3. Recognize that the underlying probability of adverse events in the population studied exerts a critical influence on the magnitude of absolute risk reduction; use this information to target treatment to subpopulations of patients most likely to benefit from treatment.
4. Use estimates of the general magnitude of effectiveness when weighing the advantages

and disadvantages of preventive treatment for individual patients and when setting clinical priorities.

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