The introduction of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in the United States coincided with the massive “know your number” cholesterol awareness campaign. For both physicians and patients, these drugs offered a powerful solution to a problem that was being deeply impressed on the public consciousness. Besides dramatically decreasing levels of low-density lipoprotein (LDL) cholesterol, statins were more convenient and better tolerated than older therapies, such as bile acid–binding resins and niacin. Their popularity was immediate, and they soon accounted for billions of dollars in revenues. Atorvastatin, for example, surpassed $1 billion in sales during the year after its introduction, even though it was approved for use in the United States many years after other statins had become established therapy.

Although statins represented a breakthrough in lipid management, questions about their role emerged. The importance of LDL cholesterol reduction in high-risk populations had already been widely accepted when the first clinical trials reported that these drugs were effective for secondary prevention of coronary heart disease (1) and for reduction of the risk for coronary events in high-risk primary prevention populations (2). More randomized trials were to come, yet gaps in the clinical evidence supporting widespread use of statins persisted. Notably absent from most clinical trials was adequate representation of elderly patients, in whom coronary disease is highly prevalent. Furthermore, the role of statins in treating patients at low short-term risk for coronary heart disease was controversial. With little disease to prevent, the benefits of risk reduction were necessarily limited and could be negated by even infrequent long-term adverse effects of treatment (3, 4). For the physician and the patient, the question was not whether statins were valuable overall, but whether and how they should be used in populations excluded from the trials.

Cost-effectiveness analysis can provide guidance for such decisions. Although much of its popularity stems from its convenience as a tool for balancing costs and benefits of treatments, diagnostic tests, and preventive interventions, cost-effectiveness analysis can do more. It offers a structured, explicit approach for combining data from multiple sources and for answering “what if” questions. Thus, for example, it can be used to extrapolate effectiveness from the results of clinical trials conducted in one population to populations at lower or higher risk for illness and death. The structured modeling of cost-effectiveness analysis makes this approach a useful adjunct to clinical trials even when costs are ignored.

Two well-conducted studies in this issue illustrate this application of cost-effectiveness analysis. Both evaluate statin use in clinically important populations that were not studied adequately in randomized trials. Ganz and colleagues (5) assessed the cost-effectiveness of statins for secondary prevention in patients 75 to 84 years of age. By assuming that the relative risk reduction from statin use in these patients is similar to that observed in the somewhat younger population in the Cholesterol and Recurrent Events trial (6), Ganz and colleagues showed that statins are both effective and cost-effective when used for secondary prevention.

Prosser and associates (7) asked similar questions about the cost-effectiveness of statins when they are used to treat diverse patients: men and women of various ages, with various cardiac risk profiles, with LDL cholesterol levels of 4.1 mmol/L or more ($\geq 160$ mg/dL), for both primary and secondary prevention of coronary heart disease. Although randomized, controlled clinical trials included some of these subgroups, none of the trials individually and none of the pooled analyses of all the published trials lend themselves to an analysis of so many finely defined subgroups.

Prosser and associates (7) showed that statins are cost-effective when used for secondary prevention but not, in most instances, when used for primary prevention. Therapy with statins did not reach a cost-effectiveness ratio of $50,000 per quality-adjusted life-year in any of the 240 risk subgroups in the primary prevention component, and only one fourth of the risk subgroups reached the threshold of $100,000 per quality-adjusted life-year. Only in the presence of multiple risk factors would statins be considered cost-effective even at this threshold. Furthermore, at 35 years of age in men and 45 years of age in women, treatment of an elevated cholesterol...
level with anything other than diet is unlikely to be cost-effective unless other risk factors are present (7). Even with other risk factors, neither statin nor niacin treatment approaches conventional levels of cost-effectiveness in patients younger than these age thresholds. Prosser and associates’ results are direct consequences of the epidemiology of coronary heart disease. In a low-risk population, a preventive intervention can be cost-effective only if it is very inexpensive.

Findings such as these come as no surprise to physicians familiar with the epidemiology of coronary heart disease, but are they valid? Both studies extrapolate from randomized trials by assuming that the relative reduction in risk for coronary disease observed in the trial populations applies to other populations. They do not consider long-term adverse effects of treatment or, for that matter, benefits delayed beyond the observation period of the trials. The actual benefits of statins might therefore differ from the benefits assumed in these studies. A randomized trial in each of these populations, if it followed enough patients for enough years, would provide the most convincing evidence of effectiveness and the most compelling estimates of cost-effectiveness. But in the absence of such a trial, the approach taken by Ganz and Prosser and their colleagues has important virtues. It directly estimates effectiveness in the study populations on the basis of reasonable assumptions, and the sensitivity analyses demonstrate whether the findings are likely to differ if the specific assumptions are not precisely correct. Studies such as these cannot establish whether statins are effective—they base this assumption on the results of clinical trials. But their methods are far superior to less formal methods in estimating the magnitude of potential benefits.

The results of the studies by Ganz and Prosser and their colleagues support the concept, implemented in the National Cholesterol Education Program’s recommendations and other guidelines, that treatment with cholesterol-lowering drugs should be targeted to patients who have an elevated risk for coronary disease on the basis of both the lipid profile and other risk factors (8). They also support the rationale underlying the screening guidelines of the American College of Physicians (ACP), which recommend screening for adults who would undergo specific management (beyond the dietary recommendations made to all adults) on the basis of the results of lipid tests (9). The ACP guidelines call for cholesterol testing in all adults with known coronary heart disease, without any age limitation. The guidelines also state that for primary prevention, screening is appropriate starting at 35 years of age in men and 45 years of age in women, and at earlier ages if other risk factors are present. Prosser and associ-ates’ results suggest that the ACP guidelines would lead to testing of almost all men and women in whom drug therapy would be cost-effective (7).

These studies reinforce the message that lipid management for secondary prevention should be a high priority, regardless of whether the patient is female or male, young or old. In the absence of multiple cardiac risk factors, statin therapy is far less cost-effective when used for primary prevention, particularly if high-risk patients receive other preventive therapies, such as aspirin (10). As we make progress in identifying effective new strategies for the prevention of coronary disease, these conclusions may need modification. For example, imaging techniques, including carotid ultrasonography, ultrafast cardiac computed tomography, and magnetic resonance imaging, are being assessed for their ability to detect atherosclerosis. If they are successful, they will help direct preventive efforts toward the patients who are most likely to benefit. Trials are evaluating the effectiveness of alternative preventive interventions, such as folate supplementation, that may reduce risk independently of cholesterol-lowering drugs. If these interventions prove to be cost-effective, the role of statins will change. Another important consideration is the changing costs of statins. As both studies show, the cost-effectiveness of therapy depends directly on the prices of the medications. If, as expected, patent expiration leads to a decrease in statin prices, the cost-effectiveness of these drugs in all patient populations will improve. For all of these reasons, strategies for the prevention of coronary disease will continue to evolve. For the time being, though, prudent—and cost-effective—practice means continuing to pursue a targeted approach to lipid management.

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References


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“Ah, I see your confusion,” Ghani said, his poisonous smile broadening. “You Europe-returned chappies forget certain things. Doctor Sahib, my daughter is a decent girl, it goes without saying. She does not flaunt her body under the noses of strange men. You will understand that you cannot be permitted to see her, no, not in any circumstances; accordingly I have required her to be positioned behind that sheet. She stands there, like a good girl.”

A frantic note had crept into Doctor Aziz’s voice. “Ghani Sahib, tell me how I am to examine her without looking at her?” Ghani smiled on.

“You will kindly specify which portion of my daughter it is necessary to inspect. I will then issue her with my instructions to place the required segment against that hole which you see there. And so, in this fashion the thing may be achieved.”

“But what, in any event, does the lady complain of?”—my grandfather, despairingly. To which Mr. Ghani, his eyes rising upwards in their sockets, his smile twisting into a grimace of grief, replied: “The poor child! She has a terrible, a too dreadful stomachache.”

“In that case,” Doctor Aziz said with some restraint, “will she show me her stomach, please.”

Salman Rushdie
Midnight’s Children
New York: Penguin; 1991:19

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