Primary Prevention of Coronary Heart Disease With Statins
It’s Not About the Money

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In the current issue of Circulation, Lazar et al report the results of their modeling of the cost-effectiveness of alternative statin treatment strategies for primary prevention using low-cost, lower-potency generic statins. Lazar’s study informs clinical decisions and practice guidelines about the potential use of statin therapy in people at low to moderate risk for coronary heart disease. It also provides an opportunity to consider the appropriate use and potential misuse of decision models to inform and guide clinical practice, and it highlights research opportunities, challenges, and potential limitations of comparative effectiveness, as well.

Statin Therapy for Primary Prevention: It’s Not About the Money
Patients and providers commonly express the desire to make medical decisions solely on the basis of anticipated clinical benefits, harms, and patient preferences and values, without considering the distorting effects of cost. With the widespread availability of generic forms of most US-licensed statins (as of November 2011, rosuvastatin will be the only Food and Drug Administration-approved patent-protected statin in the United States), the cost of statin therapy has dropped precipitously. All currently available generic statins, with the exception of simvastatin 80 mg, can be purchased for as little $0.11 to $0.13 a pill at 1 or more major national pharmacy chains.

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At these acquisition costs, Lazar et al find that low/moderate potency statin therapy is cost saving for those without a prior cardiovascular event at a moderately high risk of experiencing a coronary heart disease (CHD) event (10% to 20% over 10 years; 2 Framingham Heart Study [FHS] risk factors and a low-density lipoprotein-cholesterol [LDL-C] >100 mg/dL), and those with 2 risk factors but a <10% 10-year risk whose LDL-C is >130 mg/dL, as well. They further identify a cost-effective maximum impact strategy that comprises all people with 2 Framingham risk factors, regardless of 10-year FHS risk or LDL-C level, those with 1 FHS risk factor and LDL-C >100 mg/dL and anyone without any FHS risk factors with an LDL-C >130 mg/dL, as well. Thus, the analysis supports greatly expanding the use of statin therapy in adults (≥35 years of age).

Clinical decisions are driven by anticipated benefits, harms, costs, and patient preferences and values. As these decision inputs change, so do the thresholds for initiating an intervention or testing. The current National Heart, Lung, and Blood Institute Adult Treatment Panel-III cholesterol management guidelines explicitly were derived in part on the basis of the 2001 costs of statin therapy and the resulting estimates of cost-effectiveness. Prior statin therapy cost-effectiveness sensitivity analyses consistently have demonstrated a strong, direct relationship between statin acquisition cost and the cost-effectiveness of therapy. Thus, in the absence of new clinical evidence to the contrary, the recent substantial decline in US statin acquisition costs supports decreasing statin treatment thresholds. Indeed, this question is being addressed in National Heart, Lung, and Blood Institute Adult Treatment Panel-IV cholesterol guideline committee deliberations currently underway, along with an intensive, rigorous systematic review of the evidence base.

“All Models Are Wrong, but Some Are Useful”
Models are representations of reality. They involve a complex yet inherently simplifying series of often interrelated assumptions about pathways, processes, states of nature, and data inputs. When well constructed, conducted, and carefully interpreted, models can be useful. Models are important tools that enable the exploration of conditions and scenarios that cannot be observed or fully manipulated in nature, and thus can be useful aids to improved clinical decision making until the results of direct experiments are available or when such randomized, controlled trials (RCTs) are not feasible (in a timely or practical fashion). Decision models are explicit, formal, structured, quantitative decision support systems that protect against many heuristics, biases, and cognitive errors. They anticipate future actions and consequences and are most useful when there are several alternative possible courses of action, considerable uncertainty surrounds important decision variables, and outcomes are not known, but decisions must be made. They have a clinical starting point, consider all relevant variables and alternative actions, estimate the probability of events, specify the consequences of actions, and estimate the value of the outcomes. They are able to synthesize and integrate a wide range of the highest-quality data available, whatever their source. And, most importantly, models are flexible, allowing exploration of the impact of alternative variable specifications.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.111.040329

*See reference 4.
This latter characteristic lies at the heart of the potential value of models to inform clinical decision making. Clinical decisions inherently involve decision making under conditions of uncertainty. Too often models are used in an effort to provide answers for a clinical decision. But because models inherently are wrong, their greatest value lies in their ability to explore the range of uncertainty (for a decision input or range of inputs) that can exist before a decision threshold is crossed and the optimal decision changes. Thus, sensitivity analyses inform the nature of disagreements and important decision uncertainties; evaluate their impact on benefits, harms, costs, and preferred actions; bound estimates of the degree of confidence in results; and identify priorities on which to focus future research to resolve decision uncertainties. This is especially important for medical decision making, where data always are incomplete, often not completely consistent, and sometimes conflicting; technology frequently is changing; and patients and clinicians values often differ. Thus, decision models generally are most useful not for identifying the single correct answer, but for identifying under what conditions and for what individual values alternative management options are preferred.

The analyses performed by Lazar et al used the CHD Policy Model, a computer-simulation, state-transition model of adult (≥35 years of age) US CHD incidence, prevalence, mortality, and costs. As noted earlier, models inherently require assumptions. For example, major harms from long-term statin therapy are unknown and must be estimated. Similarly, all clinical trials are time limited in duration, with most statin RCTs 5 to 8 years in duration. Thus, the results of RCTs must be extrapolated to longer, more clinically relevant time frames (30 years in the Lazar study). Models that have been validated by their ability to predict known relationships, outcomes, events, and, ideally, the results of studies conducted subsequent to the model’s development, increase one’s confidence in a model. The CHD Policy Model is such a model, having been well validated in a variety of independent studies.

The findings reported by Lazar et al build on previous studies of the cost-effectiveness of statins in primary prevention, including prior analyses of low-cost generic statin therapy, by using current US costs and, as did the previous National Collaborating Centre for Primary Care and National Institute for Health and Clinical Excellence economic analysis, incorporating the impact of quality of life in their base case and conducting extensive sensitivity analyses to explore the conditions under which statin cost-effectiveness decreases. In doing so, they inform both clinical decisions and evidence-based practice guidelines.

Importantly, the reported findings are robust to a wide range of variations of key decision inputs, including statin adverse events. However, the results are moderately sensitive to the disutility an asymptomatic patient may place on taking a daily preventive statin for the individual probability of potential future benefit. And, of course, the model inherently depends on one’s interpretation of the clinical evidence base (eg, the maximum impact strategy is not cost-effective if statin effectiveness in reducing CHD events is <62% of that assumed in the base case analysis). In other words, at current statin costs, the decision at what level of risk to initiate statin therapy in adults for primary prevention is almost solely a function of one’s estimate of clinical effectiveness, harms, and patient preferences and values for the therapy and its side effects; statin acquisition costs are largely irrelevant.

The authors framed their analyses in the context of Adult Treatment Plan III cholesterol guidelines to estimate the incremental clinical benefits that either save costs or can be achieved at an acceptable level of cost-effectiveness resulting from decreased statin prices. Unfortunately, by focusing exclusively on the CHD risk and the LDL-C level at which statin therapy should be initiated, rather than by basing treatment decisions on global cardiovascular disease (CVD) risk or considering the alternative management strategies of fixed dose versus treatment to target, the authors missed the opportunity to inform several important clinical questions.

As such, the model estimates hard CHD risk (nonfatal and fatal myocardial infarction), with statin treatment effects driven by LDL-C thresholds. But, as the authors realize and, indeed, comment on, the world has moved on in the decade since the Adult Treatment Plan III cholesterol guidelines were crafted. Cardiovascular risk (including fatal and nonfatal acute myocardial infarction, nonfatal unstable angina, ischemic cerebrovascular disease, peripheral vascular disease, heart failure, and deaths from these causes and, indeed, all causes) is a more relevant metric, where the goal of dyslipidemia therapy is reducing risk of a CVD event, extending longevity, and increasing quality of life.

Although, at times, patients and physicians target prevention toward a specific cardiovascular risk (eg, acute myocardial infarction or cerebrovascular accident), in general, the primary clinical goal is prevention of any major CVD event. Multivariable global CVD risk assessment avoids overlooking those at high risk with multiple marginal risk factors, avoids unnecessary focus on persons with only a single isolated risk factor, and avoids the overestimation of population-attributable risks associated with individual risk factors. Consideration of CHD as opposed to CVD risk underestimates population benefit and cohorts in which preventive statin therapy can either result in net savings or be provided cost-effectively. Moreover, a single, simple calculation of CVD risk may increase physician adherence compared with the current, more complex Adult Treatment Plan III cholesterol guidelines.

The analyses by Lazar et al may underestimate the expanded benefit of statin therapy for primary prevention. In addition to the failure to consider non-CHD CVD benefits of statin therapy, the analyses examined the clinical and cost-effectiveness of low/moderate intensity statins (fluvastatin 40 mg, lovastatin 20 mg, pravastatin 20 mg, and simvastatin 10 mg), but neglected to explore the greater clinical and economic benefit of more potent simvastatin 40 mg, even though that formulation can be purchased at 1 or more national chains at a unit price similar to that of the less potent statins included in the model. When generic atorvastatin becomes available later this year, statin therapy for primary prevention may become yet more cost-effective.

As useful as the analyses by Lazar et al are, they still leave several important questions unanswered. The current analyses published in this issue do not explore when to initiate statin therapy (ie, the clinical and economic impact of early versus delayed initiation) or the incremental clinical and cost-
effectiveness of titrating therapy to treat-to-goal as opposed to fixed dose strategies (given that risk reduction is proportional to absolute LDL-C reductions and independent of baseline presenting LDL-C level).10,11

Lessons for Comparative Effectiveness Research: “In Theory There’s No Difference Between Theory and Practice. But, in Practice, There Is”†‡

As the United States gears up for a major comparative effectiveness research initiative, statin therapy for primary prevention of CVD events is an instructive case study that should be examined to determine the scope of the challenges, identify realistic expectations, and inform investments and expenditures.

The efficacy and safety of statin therapy is one of the best studied medical interventions, involving tens of thousands of patients in multiple RCTs spanning almost a quarter of a century and characterized by an unusual level of cooperation and collaboration among the investigators of individual studies. The diseases are among the most common; the underlying pathology and associated diseases are relatively well understood in comparison with many other chronic diseases. Compared with many interventions, statins are characterized in large part by very similar class effects, differing primarily in potency, without the challenges of uncertain mechanisms of action and evolving technology common to medical devices, and behavioral, organizational, and system delivery interventions. The results of the various studies have been largely consistent with one another.

Yet, although much is known, a number of important clinical issues remain unanswered. Multiple, rigorously designed and conducted multisite, multinational RCTs including a spectrum of patients and risk groups have demonstrated and quantified the benefits of statin therapy, but important questions, such as optimal methods for risk assessment, treatment objectives and strategies (eg, treating to goal versus fixed dose therapy; timing to initiate primary prevention statin therapy), overall mortality benefit in primary prevention, and important information about adverse events, remain controversial. This underscores that studies suitable for some types of decisions are unlikely to be sufficient for other decisions and decision makers, that absolute (as opposed to relative) risk reduction drives study application to practice and policy,12 and that even the most rigorous RCTs will be unable to address some important clinically relevant questions. Thus, the necessary expansion of RCTs in their various forms will not reduce, but rather increase, the need for rigorous, valid observational, quasi-experimental and data integration and synthesis studies, such as the one reported in this issue, requiring concurrent investment in developing improved nonexperimental methods if CER’s objective is to be achieved.

Disclosures

Dr Schwartz has independent, investigator initiated research grants from the National Heart, Lung and Blood Institute, National Cancer Institute, National Institute on Aging, and Pfizer. Dr Schwartz has received educational training support grants from the Agency for Health Research and Quality, National Science Foundation, National Institute of Diabetes, Digestive and Kidney Diseases, and the Robert Wood Johnson Foundation. Dr Schwartz has served as a scientific advisor for and received consulting honoraria from Abbott, Allergan, Amgen, Bayer (≥$10,000 in value over the past two years), General Electric, Genentech (≥$10,000 in value over the past two years), Johnson & Johnson, Mathematica, Merck (≥$10,000 in value over the past two years), National Committee on Quality Assurance, Sanofi-Aventis (≥$10,000 in value over the past two years), Shire, and UBCC (≥$10,000 in value over the past two years). Dr Schwartz serves on the national advisory committees of the Robert Wood Johnson Foundation Harold Amos Medical Faculty Development Program and the Association University Radiologists General Electric Radiology Research Academic Fellowship Program. He is a member of the United States Preventive Services Task Force, the National Heart, Lung and Blood Institute Cholesterol Guideline Update Committee (ATP IV), Integrated Cardiovascular Risk Reduction Guideline Committee, and Risk Assessment Work Group, the Medicare Development and Coverage Advisory Committee, the BlueCross BlueShield Association Technology Evaluation Center Medical Advisory Panel, the Institute of Medicine Committee of Medical Experts to Assist Social Security on Disability Issues, and the ECRI Institute Board of Trustees.

References


Key Words: Editorials ▪ coronary artery disease ▪ cost-benefit analysis ▪ lipids

†J.L.A. van de Snepscheut, personal observation.