Evaluating the Cost-Effectiveness of Statins

It is not easy to synthesize the available evidence on medication pricing, treatment costs, drug safety, potency, outcomes evidence, and epidemiology to derive appropriate and cost-effective treatment guidelines for hypercholesterolemic patients. Cost-effectiveness analyses that consider only narrow intermediate measures of clinical effectiveness to derive cost per percentage low-density lipoprotein (LDL) reduction ignore many key issues. They simplify away many of the factors that should be considered by clinicians and health plans in attempting to obtain value for money spent on lipid therapy. For each lipid medication, these factors should certainly include (1) the available disease outcomes evidence from randomized controlled studies (RCTs), (2) the safety evidence from RCTs and from actual market usage, and (3) given that hypercholesterolemia is a lifetime chronic condition, the potential impacts of generic competition on treatment costs.

We are only beginning to see the results of comparative trials of competing statin agents. To infer that there is a direct proportional relationship between LDL lowering and potency (even holding other coronary heart disease [CHD] risk factors constant) and CHD event reduction across statins, without head-to-head trials, is to take a leap of faith. As discussed by Sacks et al. for the Cholesterol and Recurrent Events (CARE) study, pravastatin (Pravachol) appeared to reduce CHD events as much or more in the Scandinavian Simvastatin Survival Study (4S)-eligible CARE study population as simvastatin (Zocor) did in the 4S for comparable patients, even though pravastatin did not lower LDL cholesterol (LDL-C) as much in CARE as simvastatin did in 4S.2,3

The first head-to-head trial—PROVE IT—(pravastatin versus atorvastatin) to evaluate actual CHD endpoints will be released early in 2004.4 However, based on invasive ultrasound measurement of atherosclerotic plaque progression, a smaller Cleveland Clinic study of 502 patients with preexisting CHD presented at the most recent American Heart Disease conference found that atorvastatin (Lipitor) halted CHD progression, while pravastatin did not.5 Hopefully, additional active-drug RCT comparison trials will enhance our understanding and better guide therapy choices.

The National Cholesterol Education Program (NCEP) cholesterol treatment guidelines and LDL targets are designed to be used by clinicians as simple indicators for initiation of therapy. The NCEP guidelines do not recommend specific medications nor do they predict the mortality and CHD morbidity outcomes associated with alternative cholesterol medications. They cannot be overinterpreted to provide more evidence than the existing and extensive randomized controlled trial data on statins and other lipid therapies. One cannot infer from NCEP guidelines that because one statin is less expensive than another for a given patient in “reaching the NCEP LDL goal” that it is a more cost-effective treatment. Only head-to-head RCTs comparing actual medications can establish such definitive results.

Even setting aside differences in statin medication outcomes, a reduction in LDL-C to 131 mg/dL will have about the same effect on CHD risk as a reduction to 129 mg/dL, but the NCEP effectiveness metric would consider the former as a “failure” and the latter as a “success” in achieving target LDL-C. Ironically, if managed care organization quality metrics (e.g., health maintenance organization report cards) focus on arbitrary NCEP LDL-C guidelines, physician, pharmacist, and other medical resources may be wasted on monitoring to ensure a maximum number of patients achieve these arbitrary LDL targets (e.g., by ensuring that patients slightly above LDL targets are brought under the targets) while high risk “failed” patients may be ignored. The result could easily be more heart disease than if medical resources were explicitly allocated to maximize CHD risk reduction in the managed care organization patient population.

If a clinician really believed that LDL reduction is the only thing that matters, then over-the-counter (OTC) niacin would dominate any statin on the basis of price per LDL lowering. Niacin is potent, cheap, and available without prescription (niacin 300 mg costs $0.03 per day, reduces LDL cholesterol by 17%, and raises high-density lipoprotein cholesterol by 27%). Diet is available even more cheaply, and diet can achieve a 10% to 20% LDL reduction. Compliance is a concern with all lipid therapies, including statins. While compliance is more problematic with diet or niacin, a stepped-care approach with patients initiating niacin therapy and then switching to lovastatin if niacin cannot be tolerated has been found to be economically viable and dominates statin therapy alone.15 Unfortunately, RCT data on disease outcomes with niacin or with (niacin + statin) stepped-care regimens is extremely limited.

Rosuvastatin (Crestor) is a potent statin and achieves favorable cost-per-LDL results at higher LDL reduction targets. However, in comparison with well-established statins, there is limited evidence on rosuvastatin safety over longer terms and in large populations.16 The last new potent statin on the market was cerivastatin (Baycol), and it was withdrawn after 3 years on the market due to safety concerns (which went undetected in the premarketing clinical trials). While there is no reason to assume that rosuvastatin will have a similar fate, additional value should be incorporated in any cost-effectiveness study for those statins with millions of patient-years of history of safe use, given that one potent statin has already failed in the market. For example, the difference in daily price of atorvastatin 80 mg (LDL-C reduction 60%/$3.07) and rosuvastatin 40 mg (LDL-C reduction 63%/$2.22) is $0.85.17 For many patients and providers, this $310 annual price differential could be a small premium to pay for atorvastatin’s proven safety record in millions of patients worldwide during the past decade and for its proven CHD outcomes evidence.17

Generic competition will have an increasingly important effect on the statin therapy market. Morrison and Glassberg’s analysis shows generic lovastatin 10 mg to already be a domi-
nificant treatment for lowering LDL cholesterol by 25% or less.\textsuperscript{1} This result is underscored by the favorable heart disease reduction and safety evidence for lovastatin developed in the AFCAPS/TEXCAPS clinical trial and its world-wide safety record since its market introduction in the mid-1980s.\textsuperscript{12} The majority of Americans requiring medication to lower cholesterol under NCEP guidelines fall into this moderate LDL-lowering category.

However, the price of generic lovastatin can be expected to fall dramatically over the next few years. Generic lovastatin was FDA-approved in 2002. During the first 6 months following patent expiration, the FDA allows only the first approved generic manufacturer to compete with the brand name (in this case, Mevacor). This first competitor has little incentive to lower prices (particularly published average wholesale price [AWP]). After this point, many generic competitors are allowed into the market, and the generic prices drop precipitously, usually by 70% or more when 8 to 10 generic competitors are available.\textsuperscript{17} This should happen fairly soon in the statin market.

It would be misleading to use 2003 generic lovastatin prices to talk about the cost of lifetime lovastatin therapy. Under any reasonable scenario over the next few years, generic lovastatin will dominate other statin therapies on a cost-per-LDL-lowering basis, except in high-LDL patients who can’t achieve treatment goal on lovastatin monotherapy. In the United States, these patients comprise fewer than 20% of those at risk.\textsuperscript{19}

According to Morrison and Glassberg,\textsuperscript{1} lovastatin 40 mg achieves a 31% reduction in LDL cholesterol at a cost of $1.97 per pill (per day). With 10 generic competitors, and a 70% discount resulting from generic competition, this price can be expected to drop to only $0.50 to $0.70 per day in the near future. Rosuvastatin can achieve a 63% LDL reduction at a cost of $2.22 per pill (per day). But by further combining generic lovastatin (10 mg to 40 mg) with diet, OTC niacin, generic gemfibrozil, or generic bile acid resins, patients will be able to achieve even greater LDL reduction than this, with proven safe and effective therapies at a cost substantially lower than with the relatively new and unproven rosuvastatin. Even factoring in $200 to $400 per year for compliance, tolerability, and safety monitoring, a stepped-care combination regimen with these older medications would be less expensive than rosuvastatin—not to mention that, in an increasingly competitive statin market, all manufacturers are willing to consider substantial discounts from AWP or other published drug pricing sources for preferred customers.

In a meta-analysis of statin outcomes evidence, Larosa et al. found that the proportional risk reduction in coronary events (31%; 95% CI: 26% to 36%), cardiovascular deaths (27; 95% CI: 19% to 34%), and all-cause mortality (21%; 95%CI: 14% to 28%) is roughly equivalent across primary and secondary prevention clinical trials of statin therapy, despite differences in statin potency and baseline annual cardiovascular disease risks ranging from 1.1% (AFCAPS/TexCAPS) to 5.2% (4S).\textsuperscript{19} These outcomes results are further underscored by the more recent RCT findings from the ASCOT, PROSPER, and Heart Protection Studies.\textsuperscript{7,13,14} There is no evidence that this proportional risk reduction changes with patient age, gender, or underlying cause of cardiovascular disease risk (e.g. diabetes, smoking, hypercholesterolemia, etc.).\textsuperscript{19} While such outcomes evidence has already been established for several of the available cholesterol medications, it needs to be verified for all statin medications and further refined in head-to-head statin comparison trials. Given the ranges of confidence intervals for CHD endpoints in the various statin trials, it is spuriously precise to claim that medications that achieve different LDL reductions per dollar spent translate into specific cost-effectiveness differences.

Given these meta-analysis results, Figure 1 summarizes my estimates of the current relationship between statin prices and statin cost-effectiveness as a function of baseline annual coronary event risk, assuming a 30% CHD event reduction with a statin treatment.\textsuperscript{19,20} Figure 1 suggests that, at a price of $0.50 per day, generic lovastatin (or other therapy) will be cost effective for any patient with annual CHD risk exceeding 0.5% per year, and cost saving (i.e., reduces average direct medical costs) for patients with annual CHD risk exceeding 1.5%. Since these risk categories includes millions of American adults who are not currently receiving therapy, it is important to ensure that any statin therapy administered to such large numbers of patients has solid evidence of safety and CHD event reduction.

Increased generic and brand competition in the statin and cholesterol medication markets will dramatically lower the price of these medications in the near future. This is excellent news because many of these drugs do have a good track record of safe-
ty, efficacy, and effectiveness. Saving lives with statins is increasingly one of the greatest pharmaceutical bargains available today.

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Challenges in Evaluating the Cost-Effectiveness of Statins

The article by Morrison and Glassberg1 and the editorial by Hay2 highlight the challenges encountered when attempting to assess the cost-effectiveness of drug therapies for chronic diseases, particularly new drugs. Efficacy data from randomized clinical trials (RCTs) often pertain to intermediate endpoints in the form of surrogate markers of risk for the ultimate clinical endpoints of interest. In the case of drugs for hypercholesterolemia, intermediate endpoints in RCTs often relate to changes in serum lipids, such as low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), but the ultimate goal of therapy is to reduce the risk of coronary heart disease (CHD) events. In cost-effectiveness analyses, it is common practice to use risk prediction models such as the Framingham model to translate changes in lipids into predicted changes in the risk of CHD events. However, this prediction amounts to an “educated guess” that may well be wrong. A case in point is the Women’s Health Initiative (WHI) RCT that reported that the CHD event rate in the estrogen-progesterone treatment group was 29% higher than in the placebo group over 5 years.3 The decrease in LDL-C and increase in HDL-C associated with estrogen-progesterone therapy in prior RCTs had translated into a predicted decrease in CHD event risk of about 25%.4

In the case of statins, since a relationship between LDL-C reduction and CHD risk reduction has been established for several statins, it may be reasonable to assume a “class effect” for newer statins such as rosuvastatin, at least on a qualitative level. However, using these intermediate endpoints to quantify the impact of therapy on CHD endpoints requires a leap of faith. Hay cites evidence suggesting that statins that produce the same percentage change in LDL-C need not produce the same percentage change in CHD event risk, because different statins may affect CHD risk through pathways other than LDL-C reduction. If definitive efficacy data in terms of CHD endpoints from head-to-head RCTs were available, decision models would have limited value. However, such RCTs are enormously expensive and time consuming and, as such, are rarely available,
especially for new drugs. In the absence of head-to-head CHD endpoint RCTs, a model that makes explicit “leaps of faith” has the potential to inform decision making, as long as the decision maker appreciates the limitations of the model.

While RCTs certainly represent the “gold standard” of evidence regarding efficacy, the limitations of RCTs as models for effectiveness in usual clinical practice, specifically with respect to compliance, is a crucially important issue for drug therapies targeted at chronic diseases. Hay refers to a model by Stinnett et al. that concludes that niacin dominates lovastatin as a first-line therapy for hypercholesterolemia. In this model, the authors assume essentially “ideal” compliance (discontinuation rates observed in RCTs). However, numerous studies have shown that compliance with niacin in clinical practice is poor relative to statins. This can have a huge impact on cost-effectiveness, as noted in a recent review by Hughes and colleagues. The relatively few published cost-effectiveness evaluations that attempt to assess the impact of noncompliance usually focus on discontinuation of drug therapy. In all of these studies, lower continuation rates are associated with lower incremental effectiveness. Poor compliance is associated with higher incremental cost in some studies and lower incremental cost in others, but poor compliance usually increases incremental cost-effectiveness ratios. Thus, it is quite possible that seemingly inexpensive niacin would have been dominated by the more expensive (but better-tolerated) statin in the Stinnett et al. model, if the substantial differential in compliance had been taken into account.

Another issue is the choice of an effectiveness metric to use in the denominator of the cost-effectiveness ratio. Gold et al. recommend the use of QALYs, though they acknowledge that other effectiveness measures may have value in particular settings or for particular audiences. In the case of formulary decision makers, it is common to consider “within class” cost-effectiveness issues as an adjunct to “which class” cost-effectiveness issues. In the context of statins, a cost-effectiveness ratio expressed as “cost per percent LDL-C reduction” will tend to preserve the rank-order of cost-effectiveness for alternative statins if the error is small in the projection of LDL-C change onto CHD risk change. But the results using this effectiveness metric may be difficult to interpret. For example, Morrison and Glassberg report that rosuvastatin 5 mg yields an incremental improvement in LDL-C reduction of about 6 percent over atorvastatin 10 mg, at an additional cost of about $80 in annual drug costs. What criterion may be used to conclude that rosuvastatin is (or is not) worth this additional cost?

Morrison and Glassberg also report results using the percent of patients meeting National Cholesterol Education Program III treatment thresholds as an effectiveness measure. This “treatment success” metric has an intuitive appeal and may be relevant to managed care organizations, to the extent treatment success rates are reflected in organizational quality metrics. However, similar issues of interpretation remain: What is a “reasonable” incremental cost per treatment success? As Hay notes, a related issue is that the threshold approach often employed in treatment guidelines or Health Plan Employer Data and Information Set scores can produce incentives for waste. For example, there is no meaningful difference in CHD risk for a patient with LDL-C of 131 mg/dL and a patient with LDL-C of 129 mg/dL, but incremental resources consumed to achieve “success” might have provided greater benefit elsewhere. Although this is a legitimate concern, it is not possible to base quality performance metrics on “hard” endpoints for chronic diseases because of the lag time from quality of care received to hard endpoints, coupled with the turnover in managed care populations. Managed care organizations operate in competitive markets where payers want quality metrics in one form or another. Threshold quality metrics probably will continue to be used in the absence of a viable and superior alternative. Clearly, standard effectiveness metrics like QALYs are essential to make assessments of relative value, but additional metrics may provide additional information that may be helpful to managed care organizations.

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The author discloses current work as a consultant for AstraZeneca in a study of the patterns of treatment of bipolar disorder. This research is not drug-specific and is unrelated to rosuvastatin.

REFERENCES