A Perspective on Principles of Comparative Cost-Effectiveness Studies for Pharmacotherapy of Chronic Diseases

Pendar Farahani, MD, MSc

Chronic diseases such as heart disease and diabetes are the leading causes of disability and death in the United States. Seventy percent of all deaths in the United States annually are the result of chronic diseases, and 25 million Americans live with a chronic disease that significantly limits their daily activity. Chronic diseases account for >80% of health care spending in the United States annually.

Elevated cholesterol is linked to three of the biggest killers in the United States: heart disease, stroke, and diabetes. The World Health Organization estimates that dyslipidemia is associated with more than half of the global cases of ischemic heart disease and more than 4 million deaths per year. Controlling this crucial health risk factor has a significant impact on these related diseases. For example, a 10% reduction in serum cholesterol levels can result in a 30% reduction in the incidence of coronary heart disease.

The literature on the epidemiology and economics of dyslipidemia is extensive. Many articles have been written on dyslipidemia, considering the costs of dyslipidemia alongside stroke or diabetes. These studies analyze the prevalence and costs of dyslipidemia, with a focus on analyses related to stroke and diabetes.

Comparative cost-effectiveness studies of therapeutics can accurately support decision-making in health care resource allocation if principles of clinical pharmacology and pharmacoepidemiology are considered. The objective of this article is to review previous economic evaluations of statins and highlight methodological issues that can limit the applicability of their results.

Several clinical and therapeutic factors are crucial to incorporate into comparative cost-effectiveness drug studies. Essential factors that affect the applicability of such studies include 1) bioequivalent doses of therapeutics, 2) escalating doses (up-titration), 3) data from head-to-head randomized clinical trials (RCTs), 4) community-based data of the target population, 5) evidence-based time horizon, 6) data on nonadherence and drug safety, and 7) use of hard endpoint outcomes. The following sections review each of these factors in detail.

Bioequivalent Doses
According to the American College of Clinical Pharmacy’s Guidelines for Therapeutic Interchanges, “therapeutically equivalent drugs are chemically dissimilar but produce essentially the same therapeutic outcome and have similar toxicity profiles. Usually, these drugs are within the same pharmacologic class.” For example, all 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly referred to as “statins”) generally are not equivalent on a milligram-to-milligram basis. However, estimating equivalent doses based on efficacy and safety monitoring parameters proposes an approximate dosing equivalency of statins as follows: rosuvastatin, 5 mg = atorvastatin, 10 mg = simvastatin, 20 mg = pravastatin, 40 mg = lovastatin, 40 mg = fluvastatin, 80 mg. These equivalents can be used as a dosing conversion factor in therapeutic interchange programs in clinical practice.

Economic evaluation of pharmacotherapies can accurately support decision-making in health care...
resource allocation if therapeutically equivalent doses are incorporated into the economic analysis to reflect the clinical comparability of different agents. However, this important issue was not considered in most economic evaluations of statins.

For example, the Surrogate Marker Cost-Efficacy (SMaC) study was undertaken to assess the economics of treatment with simvastatin, 10–20 mg/day, versus treatment with atorvastatin, 10–20 mg/day, in reducing LDL cholesterol in patients with hyperlipidemia, based on the results of a 1-year, double-blind, parallel-group clinical trial. However, 10–20 mg atorvastain is bioequivalent to 20–40 mg simvastatin.

In another study, the Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS), atorvastatin, 10–80 mg/day, was compared with fluvastatin, 20–40 mg/day or 40 mg twice daily; lovastatin, 20–40 mg/day or 40 mg twice daily; pravastatin, 10–40 mg/day; and simvastatin, 10–40 mg/day. Patients were started at the lowest available dose and titrated to higher doses at 6-week intervals until they achieved the National Cholesterol Education Program (NCEP)-II LDL cholesterol target or reached the highest available dose. However, this study did not take into consideration therapeutic bioequivalency.

An economic-modeled analysis based on results of the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial was conducted to evaluate the long-term cost-effectiveness of high-dose atorvastatin compared to conventional-dose simvastatin, 20–40 mg/day) for secondary prevention. The IDEAL study, an RCT, demonstrated significant reductions in cardiovascular endpoints with high-dose atorvastatin (80 mg/day) compared to conventional-dose simvastatin in patients with stable coronary heart disease. A more meaningful comparison would have been between high-dose atorvastatin and high-dose simvastatin.

Escalating Doses (Up-Titration)
Management of hyperglycemia, hypertension, and hyperlipidemia often requires escalating doses of drugs to achieve predefined goals or clinical targets. Escalating doses (up-titration) reflects pharmacokinetics and pharmacodynamics of therapeutics that are applicable to the interpretation and economic evaluation of clinical protocols in practice settings. However, several pharmacoeconomic analyses incorporated fixed, constant-dose statins from RCTs. Examples include the West of Scotland Coronary Prevention Study (WOSCOPS), which measured the efficacy of a fixed and constant dose of pravastatin (40 mg/day), and a meta-analysis of RCTs of monotherapy with fixed doses of statins.

In clinical practice, dose escalation is routinely used to achieve treatment goals. However, few economic evaluations have addressed the issue of up-titration in their models.

One example in which up-titration was used is a study by Smith et al., who conducted an economic evaluation using data from ACCESS. As mentioned earlier, in ACCESS, a 54-week RCT, patients were started at the lowest available dose of atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin and titrated to higher doses at 6-week intervals until they achieved the NCEP II LDL cholesterol target or reached the highest available dose of medication. Using ACCESS data in this economic model reflects dose up-titration, which is applicable to clinical practice.

Head-to-Head Versus Placebo-Controlled RCTs
In the development of a new drug, several studies must be completed before the drug wins approval by regulatory authorities for use in clinical practice. In phase 3 of this process, double-blind, placebo-controlled RCTs are conducted to evaluate the efficacy and safety of the drug.

Head-to-head RCTs provide meaningful data by assessing a balanced distribution of the patient population among different arms of a trial with active therapeutics. However, for the economic evaluation of a class of drugs such as statins, for which several agents have already been marketed, placebo-controlled RCTs cannot accurately evaluate the superiority of one agent over another.

Several economic evaluations of statins have used data from placebo-controlled RCTs such as the WOSCOPS, the Scandinavian Simvastatin Survival Study (4S), and the Collaborative Atorvastatin Diabetes Study (CARDS). These economic analyses are of limited use in guiding the drug therapy selection process.

Therapeutic decisions should be based on the agent and dose that can lead to superior cost-effective outcomes. However, economic analyses of comparative studies for different agents of statins have not been extensively published. These studies are needed to support formulary and drug-therapy selection decisions regarding statins.

Previous studies have compared the cost-effectiveness of different classes of lipid-lowering drugs. For example, the lifetime cost-effectiveness of statins was compared to that of fibrates for the treatment of hyperlipidemia. Estimates of lipid modification achieved because of drug therapy were based on published head-to-head comparisons of
specific statins and fibrates in randomized, double-blind studies.\textsuperscript{23} In other studies, the cost-effectiveness of simvastatin was compared to that of cholestyramine.\textsuperscript{24,25}

These head-to-head RCTs can potentially be a better estimate of balanced assessments of therapeutics compared to placebo-controlled RCTs. Koren et al.\textsuperscript{26} used data from a randomized, 54-week, multicenter, head-to-head controlled trial to compare atorvastatin to simvastatin, lovastatin, and fluvastatin. Statin therapy was initiated at recommended starting doses and increased according to NCEP guidelines and drug package insert information. For patients who did not reach the goal at the highest recommended dose of each statin, the resin colestipol was added. These economic evaluations can reflect comparisons among medication classes and combination therapies in clinical practice.

Community-Based Data of the Target Population

RCTs assess drug efficacy in a controlled and somewhat artificial clinical environment. There are narrow inclusion criteria, and patients with comorbidities, children, elderly patients, and pregnant women are often excluded. The treatment strategies are fixed by study design, and drug doses and drug combinations are defined by protocol.\textsuperscript{27,28}

In contrast, real life presents a wide spectrum of patients such that patient inclusion criteria are broad, and there are few, if any, exclusion criteria; combinations of drugs and drug doses are dynamic; and the treatment strategies are flexible and dependent on the course of the illness.\textsuperscript{27,28} Also, the treatment effect of a therapeutic agent may be different when it is used in an unselected population in clinical practice settings.\textsuperscript{29} These community-based aspects of therapeutic evaluation can be associated with the population pharmacokinetics and pharmacodynamics of drugs and may reflect pharmacogenomics\textsuperscript{30,31} and pharmacoeconomy\textsuperscript{32} of therapeutics in the target population.

The above-mentioned issues may also influence the outcomes of economic evaluation of therapeutics in community clinical practice when compared to RCTs.\textsuperscript{33,34} To achieve more meaningful results, cost-effectiveness studies should be conducted for a specific population to reflect medical patterns of practice, health care regulations, and intervention costs in the target population.\textsuperscript{35}

Several pharmacoeconomic evaluations of statins incorporated a variety of community-based aspects of statin therapy in their models. In a U.K. economic evaluation, estimates of the distribution of patients receiving each dose of statin were derived from the U.K. national Doctors’ Independent Network database.\textsuperscript{36} In a Canadian economic assessment of statins, a model based on data from the Lipid Research Clinics cohort was used to estimate the benefits and cost-effectiveness of lipid modification with statins based on results from the 4S.\textsuperscript{37} Also, Ohsfeldt et al.\textsuperscript{38} assessed the effectiveness and cost-effectiveness of treatment with atorvastatin, rosuvastatin, and simvastatin in high-risk patients in routine clinical practice, involving patients 18–79 years of age with coronary heart disease or the equivalent who initiated statin therapy. These economic evaluations reflect the use of clinical data from community practices that is applicable for a target population.

Evidence-Based Time Horizon

Economic analyses based on RCTs often focus only on the results that are observed during the study. However, for many preventive interventions such as cardiovascular risk reduction, associated costs and benefits will accumulate over patients’ remaining lifetime. Therefore, economic analyses beyond the duration of RCTs are required to fully evaluate the potential costs and benefits of long-term preventive therapies.\textsuperscript{39}

When conducting cost-effectiveness studies, the choice of time horizon has a substantial effect on the calculated incremental cost-effectiveness ratios.\textsuperscript{40} This has been illustrated in several simulation studies. For example, in a Canadian study,\textsuperscript{39} it was illustrated that the estimated efficacy and associated cost-effectiveness of ramipril is extremely sensitive to the selected time horizon. Consequently, care must be taken in choosing the time horizon in a cost-effectiveness analysis to minimize biases.

Economic evaluations with a lifetime horizon commonly use Markov models, which simulate patients’ lifespan by dividing it into equal periods (cycles). At each cycle, the model exposes a hypothetical cohort to the competing hazards of normal aging and of the disease in question (disease-specific hazards), and the results are presented as years of life expectancy. However, because there are no readily available data on changes in disease-specific hazards over time, these hazards are often derived from short-term follow-up studies and are assumed to be constant over patients’ entire life.\textsuperscript{40} When the measurement of a long-term outcome is necessary, selecting evidence-based time horizons according to pharmacoepidemiology data over hypothetical models based on life-expectancy tables is crucial.

Several pharmacoeconomic studies of statins incorporated long-term patterns in their models. For example, using data from CARDS, atorvastatin, 10 mg daily, was compared to placebo. Patients
were followed for a median period of 3.9 years and the cost per quality-adjusted life-year gained over a patient’s lifetime was calculated as one of the outcomes. In another study, it was estimated that 3–5.6 years (average 4.6 years) of statin treatment resulted in 0.15–0.41 years (average 0.3 years) saved over a lifetime horizon. Consequently, using data from short-term RCTs for economic evaluation of interventions for chronic diseases is not clinically meaningful. For example, several pharmacoeconomic assessments of statin therapy incorporated data from short-term RCTs such as the Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients with Hypercholesterolemia (CURVES) and the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin ( STELLAR) trial into their models. CURVES, a multicenter, randomized, parallel-group clinical trial, compared atorvastatin to fluvastatin, lovastatin, pravastatin, and simvastatin for a period of 8 weeks. STELLAR, a multicenter, randomized trial, consisted of a 6-week dietary lead-in period and a 6-week randomized treatment period. Patients who were compliant with the diet and met lipid criteria after the first 6 weeks were randomized for 6 weeks of statin therapy.

Therefore, economic evaluation models should incorporate a time horizon that is long enough to be clinically meaningful.

Adherence and Drug Safety
Nonadherence with drug therapies not only limits their effectiveness, but in some instances is also associated with grave clinical sequelae and substantial economic burden. For example, Bouchard et al. evaluated the impact of adherence to statins on nonfatal coronary artery disease (CAD). Nonfatal CAD events were significantly lower among patients with adherence of > 90% compared to patients with adherence of < 90% after 1 year of follow-up (relative risk 0.81, 95% CI 0.67–0.97). Nonadherence always results in a reduction in efficacy, but its impact on cost varies substantially. First, in the RCT setting, withdrawals from studies are reported to be significantly lower than in postmarketing studies. Second, the rate of nonadherence and therapeutics discontinuation in clinical practice depends on the clinical and demographic characteristics of the patients in the target population. Sex, age, level of education, comorbidities, comedications, statin dose, and indication for statin therapy (primary versus secondary prevention) can influence adherence rates. Consequently, the overall nonadherence to statins obtained from clinical settings data demonstrates a wide range of divergence.

For example, a cohort study using linked population-based administrative data from Ontario reported adherence to statins among patients > 65 years of age who received at least one statin prescription between January 1994 and December 1998. Two-year adherence rates in the cohorts were only 40.1% for patients with recent acute coronary syndrome, 36.1% for patients with chronic CAD, and 25.4% for patients without coronary disease (primary prevention).

Another study was performed using data from the Régie de l'Assurance Maladie du Québec. Persistence and adherence to treatment were estimated separately. After 24 months, the persistence rate with the statins was 83%. The proportion of patients who switched from their initial statin varied across the statins (ranging from 7 to 34%). The proportion of patients who were 80% adherent to statin therapy was 43%.

Therefore, it is important to incorporate measures of adherence from real-world compliance data into pharmacoeconomic evaluations.

Adverse events are one of the sources of nonadherence that can lead to discontinuation of therapies. Mild and severe adverse events occur for all therapeutics. Although statins are the first-line pharmacotherapy for hypercholesterolemia and have been shown to have a safe profile, in both RCTs and postmarketing observation studies, sporadic reports of serious adverse events such as hepatotoxicity and rhabdomyolysis with statins should be considered in clinical effectiveness and cost-effectiveness studies.

These adverse events may be associated with molecular properties, the dosage of statin, and its potential for drug-drug interactions. Average incidences per 10,000 person-years for monotherapy with rosvastatin, atorvastatin, pravastatin, and simvastatin were reported as < 2% for myopathy, < 0.5% for rhabdomyolysis, and < 0.5% for acute liver toxicity. Although event rates are small, routine biochemical test monitoring is recommended for statin therapy in clinical practice to detect and prevent adverse drug reactions.

Herman et al. included the cost of drug safety monitoring and adverse experiences into the calculation of the cost of simvastatin treatment. This monitoring process is associated with costs, which should be considered in cost-effectiveness analysis.

Hard Endpoints Versus Surrogate Endpoints
Endpoints are the clinically important outcomes that are measured during
clinical studies, such as the impact of therapy on health-related quality of life, morbidity endpoints such as stroke or myocardial infarction, and mortality. The clinical outcomes measured in many pharmacoeconomic analyses of statin therapy have included death, cardiac arrest, nonfatal myocardial infarction, fatal myocardial infarction, angina pectoris, nonfatal stroke, congestive heart failure, surgical or percutaneous coronary revascularizations, and the incremental cost per clinical event avoided. However, measuring clinical (hard) endpoints in studies requires long-term follow-up of a large population (sample size). In these situations, use of surrogate endpoints is helpful.

A surrogate endpoint or a biomarker is defined as “a characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” Surrogate endpoints include a wide range of laboratory or physical measurements used in clinical studies as a substitute for meaningful clinical endpoints that directly assess the effects of the interventions tested on mortality or morbidity.

Surrogate endpoints or biomarkers are often cheaper and easier to measure than hard endpoints. In clinical trials, the use of biomarkers allows for smaller sample sizes. Some economic evaluations considered biomarkers (surrogate endpoints) as outcome measures. For example, the SMaC study assessed the economics of hyperlipidemia treatment with simvastatin versus atorvastatin using LDL cholesterol as an outcome measure. In another study, a model-based economic evaluation was conducted to estimate the number of patients achieving the National Service Framework targets for LDL cholesterol and triglycerides at each dose of statin and to calculate the average drug cost and incremental drug cost per patient achieving the target levels. However, although a surrogate endpoint (or biomarker) is a measure of the effect of a certain treatment that may correlate with a hard endpoint, it does not necessarily have a guaranteed relationship.

Reliance on surrogate endpoints may be harmful and may lead to excess morbidity and mortality. Association studies using surrogate endpoints may demonstrate significant benefit for an intervention, but in fact the conclusion may not be reproducible for hard endpoints. For example, while dihydropyridine calcium channel blockers are efficacious in lowering blood pressure, their effects on clinically important outcomes such as stroke, myocardial infarction, and death are less certain. In another example, flecainide was believed to be beneficial because it reduced arrhythmias (a surrogate endpoint). However, the Cardiac Arrhythmia Suppression Trial found that flecainide increased the death rate (a clinically important endpoint).

Summary
Comparative cost-effectiveness studies of therapeutics for chronic diseases can accurately support decision-making in health care resource allocation if the principles of clinical pharmacology, therapeutics, and pharmacoepidemiology are considered. Economic evaluations of statins from numerous previous studies demonstrated several methodological limitations that diminish the applicability of these evaluations for clinical use and policy-making.

To provide clinically meaningful results that can be applied to the real-world setting, cost-effectiveness studies need to be designed to consider the principles of clinical pharmacology and pharmacoepidemiology. Incorporating therapeutically equivalent doses into the economic analysis will reflect the clinical comparability of therapeutics. Using escalating doses, or up-titration, rather than fixed doses will result in evaluations that are applicable to clinical protocols in practice settings. Using head-to-head instead of placebo-controlled RCTs will provide a more meaningful economic comparison of therapeutics that assesses a balanced distribution of efficacy and safety of medication. Economic evaluations should be conducted on a target population rather than using data from RCTs. Evidence-based time horizons using available clinical data that are clinically meaningful can provide economic information that is applicable to the real-world clinical setting. Measures of adherence with drug therapies from real-world data as opposed to RCT settings should be incorporated into economic studies to provide a more accurate reflection of the clinical and demographic characteristics of the patients in the target population. Hard endpoints, which are clinically meaningful outcomes, should be used in economic evaluations of therapeutics instead of surrogate endpoints, which are cheaper and easier to measure but not always reliable for clinically significant outcomes.

Inclusion of these factors in future comparative cost-effectiveness studies of therapeutics for chronic diseases will ensure applicability of the study results to real-world clinical settings.

REFERENCES


Tenenbaum A, Fisman EZ, Motro M: Rhabdomyolysis and lipid-lowering drugs. *JAMA* 293:1444–1449, 2005


