Pharmacoeconomics of Angiotensin Converting Enzyme Inhibitors in Heart Failure

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As a result of the increasing cost of health care and the limited resources available, it has become more difficult to allocate resources efficiently and effectively in the health care system. This environment has led to the development of pharmacoeconomic studies, which have been designed in response to the need for assessment of the economic benefits of a product prior to its acceptance in the market.

The field of pharmacoeconomics has grown rapidly, especially in relation to the development of new pharmacological products. Economic analysis is now routinely incorporated into many clinical trials, and this type of information, in conjunction with the usual safety and efficacy data, is becoming more important to pharmaceutical companies, regulatory authorities, third party payers, and end-users.

The cost-effectiveness of angiotensin converting enzyme (ACE) inhibitors for the treatment of heart failure has been evaluated on the basis of a number of large-scale studies, including the Survival and Ventricular Enlargement (SAVE) study and the Veterans Administration Cooperative Vasodilator Heart Failure Trials (V-HeFT I and II). The cost-effectiveness of the ACE inhibitor captopril compares favorably with other cardiac interventions, reducing both mortality and the incidence of congestive heart failure (CHF). Captopril also appears to be cost-effective in the treatment of patients with left ventricular dysfunction after acute myocardial infarction. In addition, analysis of more recent studies of the treatment of fosinopril in patients with mild to moderate CHF have been performed and have proved this newer ACE inhibitor to be cost-saving in these patients. Am J Hypertens 1997; 10:272S–279S © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Pharmacoeconomics, cost-effectiveness, angiotensin converting enzyme inhibitors, congestive heart failure, captopril, fosinopril.

Over the past few years, the study of pharmacoeconomics has experienced an extraordinary boom within the health care sector, as a wide range of new techniques have been developed to evaluate the economic impacts of clinical care and medical technology. Clinicians, pharmacists, economists, epidemiologists, and operations researchers have all contributed to the new field of pharmacoeconomics by studying how different approaches to patient care can influence the resources consumed in clinical medicine.

Health economists start with the basic premise that, whereas desires and needs are infinite, resources are limited. Therefore, they try to find the best way to allocate these resources appropriately in order to maximize the overall health of the population, with the
search for increased effectiveness (the impact of an intervention on outcomes) and efficiency (whether an intervention is capable of favorably affecting outcomes) of health care services and products as the common factor (Figure 1). With this in mind, several researchers, particularly within the health care industry, have begun to study the economic impact of products and services on the provision of health care. This new field of research has grown rapidly, supplying ample evidence of the economic benefits of modern diagnosis, testing, and therapy. Thus, in the current health care climate, the economic impact of new products and services needs to be established.

THE NEED FOR PHARMACOECONOMICS

Economic assessment of health care developed in response to the needs of administrators, third party payers, and politicians, who needed to understand the consequences of technological changes in health care. Decisions relating to the use of technologies used to be based entirely on the clinical safety, efficacy, and quality of the products used; however, increasing medical costs, as well as the unique burdens associated with managing chronic disease, have sensitized health care decisionmakers in both the private and public sectors to the problems of scarcity of resources and competing interventions. Now, the economic impacts of a product require assessment before it is widely endorsed.

Although numerous economic evaluations have been reported, the quality of the research and, therefore, its validity in decisionmaking has been variable. On the other hand, as techniques become more sophisticated, there is a danger that the specialized nature of the studies, which require a high level of knowledge and understanding to interpret, may alienate the decisionmakers from these analyses. Therefore, decisionmakers often require guidance on the principles and methods used, help in interpreting the studies and judging the quality of the data contained within them, and perspective in determining their applicability to a particular clinical setting.

BASIC TERMINOLOGY IN PHARMACOECONOMICS

"Cost-effectiveness" is often used to describe loosely interventions that have some economic benefits; however, formal cost–effectiveness analysis requires specific methodology to compare the total cost of an intervention with its benefit or effectiveness (ie, its impact on outcome measures). In cost–effectiveness analysis, a cost is determined per unit of outcome. Cost are those related to the intervention (eg, a pharmacological agent, a surgical procedure, outpatient visit, cost of complications) minus savings related to the prevention of events.

The most commonly used measure of effectiveness is prolongation of life, known as life-years or years of life saved, although it may also be measured by the number of lives saved. Evaluation of an intervention involves comparison with comparator interventions; these comparisons are known as “incremental” or “marginal” cost–effectiveness analyses. In an “average” cost–effectiveness analysis, total costs are divided by outcomes (such as life expectancy), without taking into account comparator strategies. Therefore, this analysis determines cost per year of life, rather than cost per year of life saved.

In a cost–benefit analysis, health benefits are given a “dollar” value, allowing a direct “dollar” comparison between different interventions. Although cost–effectiveness analysis does not take into account quality of life, cost–utility analyses address this issue, with health outcomes quantitatively expressed as quality-adjusted life years (QALY). QALY represents a reduction in the value of a healthy year caused by factors related to the disease and its treatment or complications, and has been defined as “the number of years of..."
full health that would be equivalent to the number of years of life as experienced.1,2

In developing a cost–effectiveness analysis, uncertainties and possible biases often exist in the assumptions made; however, it is important to assess how critical a given assumption is to the conclusions made. Sensitivity analysis enables the determination of how dependent the final results are on a given assumption and to what extent one or more reasonable changes in these assumptions influence the results of the analysis.1

THE BENEFITS OF PHARMACOECONOMICS

Health economic evaluations can bring benefits to various interested parties.

Third Party Payers Third party payers are able to formulate better policies and reach more informed decisions when allocating funds or negotiating contracts with health care providers. In addition, a better mix of health care services offered to the insured population can be coordinated. One of the most important advantages of pharmacoeconomics for third party payers, however, is the ability to make more informed management decisions, through a more transparent cost structure and better forecasting of demographic and epidemiologic shifts and their subsequent impact.

Health Care Providers Providers benefit from pharmacoeconomics by optimizing their mix of clinical strategies and their ability to choose from alternative services. The study of clinical economics is becoming part of the curriculum in many medical schools, and professional medical journals are publishing an increasing number of articles on the economic evaluation of new technologies.

Manufacturers Manufacturers benefit in two ways: proactively and reactively. Proactively, the industry can establish the true value and appropriateness of its products. Reactively, manufacturers can meet the demands of health care administrators, providers, and politicians for economic data. In a competitive world, all manufacturers will need to carry out such evaluations to meet the demands of their customers.

Patients Patients will have to bear more and more of the health care bill, either through copayments or by risk-adjusted insurance premiums. Therefore, their choices will be based on the perceived value of the services or products offered. In this instance, value does not simply mean the actual cost of a service or product, but it also includes patient preferences for different types of testing and treatment in addition to their expectations of health outcome. As a result, analyses of patient preferences, which include quality of life assessments, are a growing part of health economics research.

PHARMACOECONOMIC ASPECTS OF ACE INHIBITORS

Because it is a source of considerable expense, particularly in the elderly, congestive heart failure (CHF) is an important disease area for cost–effectiveness analysis. Given the high prevalence of CHF, its substantial cost and the high risk of hospitalization and readmission, interventions that produce even a small relative reduction in adverse outcomes may be worth a substantial investment. ACE inhibition with captopril and hydralazine (with a concomitant nitrate) have been demonstrated to prolong life,3–5 and ACE inhibition with enalapril also delays the development of CHF and decreases hospitalization in patients with left ventricular dysfunction.6 In addition, captopril also prevents the development of CHF following myocardial infarction (MI).7 More recent studies in patients with CHF treated with fosinopril have also shown a reduced rate of events indicative of worsening of CHF, including hospitalizations and better exercise tolerance associated with this newer ACE inhibitor.8,9

The cost–effectiveness of captopril therapy was evaluated in the Survival And Ventricular Enlargement (SAVE) study in several countries.10–12 The SAVE study7 was a double-blind, placebo-controlled trial that involved 2231 patients with left ventricular dysfunction and an ejection fraction of ≤40%, but without overt symptoms of heart failure or myocardial ischemia. Patients were randomized to receive either placebo or captopril 3 to 16 days after MI and were then followed for an average of 42 months. In the captopril group, there was a significant reduction in overall mortality (20% v 25%), death from cardiovascular causes (17% v 21%), development of CHF (11% v 16%), and recurrent MI (12% v 15%). The impact of captopril after MI was analyzed in a retrospective cost–effectiveness analysis from the perspective of the German Statutory Insurance Fund.11 Additional data, for example, the average number of days spent in hospital or average costs for hospitalization per day, were taken from nationally published statistical sources.12,13 In this cost–effectiveness analysis, inputs (monetary units) and outputs (nonmonetary units) were identified and measured. The analysis (costs per life-year gained) demonstrated a relationship between the costs for captopril treatment, costs for MI, costs for left ventricular dysfunction, and the clinical benefit (the number of life-years gained). Initially, costs in the captopril group were over US$ 2 million higher than in the placebo group (calculated from 3.7 million DM using a calculation factor of 0.58), but these costs were partly compensated for by the costs saved through the reduction in MI (US$ 1,254,483 [DM 2,162,901]) and left ventricular dysfunction and CHF (US$ 322,780 [DM 556,518]). The clinical benefit for the captopril
TABLE 1. COMPARISON OF THE COST-EFFECTIVENESS OF VARIOUS INTERVENTIONS FOR PATIENTS WITH CORONARY HEART DISEASE

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost-Effectiveness (US$/YOLS)</th>
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<tbody>
<tr>
<td>Captopril in diabetic nephropathy</td>
<td>&lt;0*</td>
</tr>
<tr>
<td>ACE inhibitor treatment of CHF</td>
<td>&lt;0*</td>
</tr>
<tr>
<td>Smoking cessation program after acute MI</td>
<td>220</td>
</tr>
<tr>
<td>β-Blockers after MI</td>
<td>3,200–18,400</td>
</tr>
<tr>
<td>Captopril treatment after MI</td>
<td>14,062–17,796</td>
</tr>
<tr>
<td>Thrombolysis in elderly with suspected acute MI</td>
<td>21,200–22,400</td>
</tr>
<tr>
<td>CCU admission for patients with 5% to 20% probability of acute MI</td>
<td>78,000–328,500</td>
</tr>
</tbody>
</table>

Adapted from Tsevat et al.10

YOLS, years of life saved; CCU, coronary care unit; MI, myocardial infarction; ACE, angiotensin converting enzyme; CHF, coronary heart failure.

* <0, money is saved.

treatment equated to 495 life-years gained. The cost-effectiveness ratio was US$ 1160 (DM 2000) per life-year gained. The results of this analysis show that treatment with captopril after acute MI is not only clinically efficacious, but also cost–effective.11

In the United States, another analysis of the SAVE data was performed.10 Because it is not yet known whether the benefits of captopril therapy persist beyond 4 years, two sets of analyses were made: one assumed that the survival benefits associated with captopril therapy would persist beyond 4 years (persistent-benefit analysis) and the other assumed that captopril therapy incurred costs, but no survival benefit beyond 4 years (limited-benefit analysis). In the persistent-benefit analysis, the incremental cost-effectiveness ranged from US$ 3700 to US$ 5600/QALY gained for patients aged 60 to 80 years old and US$ 10,400/QALY gained for 50-year-old patients. In the limited-benefit analysis, cost-effectiveness was similar to persistent-benefit analysis for 80-year-old patients (US$ 3600/QALY gained). Because 50-year-old patients have more years of life remaining, cost would be much higher if the benefits of captopril were not persistent (US$ 60,800/QALY gained). Therefore, the cost-effectiveness of captopril therapy depends on the age of the patient and whether the benefit of captopril is limited or persistent, although it is unlikely that there is a cessation in the benefit of captopril therapy after 4 years.10

The cost-effectiveness of captopril therapy compares favorably with many other cardiac interventions; for example, US$ 3200 to US$ 18,400/year of life saved with β-blockers after MI15 and US$ 21,200 to US$ 22,400/year of life saved using streptokinase in suspected acute MI in elderly patients.16 Thus, ACE inhibitor therapy not only reduces mortality and the incidence of heart failure, but is also cost–effective in patients with asymptomatic left ventricular dysfunction following an acute MI (Table 1). However, it is uncertain whether these findings can be extrapolated to patients with asymptomatic left ventricular dysfunction secondary to idiopathic cardiomyopathy.

Three randomized, multicenter trials have evaluated the role of vasodilator or ACE inhibitor therapy in patients with CHF.4–6 In V-HeFT-I (Veterans Administration Cooperative Vasodilator Heart Failure Trial),4 642 men with CHF who were taking digoxin and a diuretic were randomly assigned to receive additional double-blind treatment with placebo, prazosin, or a combination of hydralazine and isosorbide dinitrate. The mortality rate in the prazosin group was similar to that in the placebo group. The group receiving hydralazine and isosorbide dinitrate had a 36% risk reduction after 3 years and an improvement in left ventricular ejection fraction. In the Studies of Left Ventricular Dysfunction (SOLVD) trial,6 patients with CHF receiving conventional treatment were randomly assigned to receive either placebo (n = 1284) or enalapril (n = 1285). When compared with placebo, enalapril significantly reduced total mortality (39.7% v 35.2%), death due to progressive heart failure (19.5% v 16.2%), and hospitalization for cardiovascular causes (63% v 57%). The V-HeFT-II trial5 compared the effects of hydralazine and isosorbide dinitrate with those of enalapril in 804 men receiving digoxin and diuretic therapy for CHF. Mortality after 2 years was significantly lower in the group receiving enalapril than in the group receiving hydralazine and isosorbide dinitrate (18% v 25%). The data from these three major trials have been used to evaluate the cost-effectiveness of vasodilator therapy for heart failure.

A decision analysis model, in which the probability and outcomes of interventions are quantified, was used to evaluate the cost-effectiveness of adding the hydralazine–isosorbide dinitrate combination or enalapril to standard therapy with digoxin and diuretics.17 The incremental cost-effectiveness was calculated as the cost of the new treatment per unit of improved outcome, compared with the usual standard of care.1 An incremental expense of US$ 5600/
year of life saved was found for a patient receiving hydralazine–isosorbide dinitrate therapy and US$ 9700 for enalapril therapy. These costs compare favorably with other accepted preventive measures; for example, US$ 25,000/year of life saved with the treatment of hypertension and US$ 18,400/year of life saved with β-blocker therapy after MI. The authors of this paper concluded that, although the cost per year of life saved for hydralazine–isosorbide dinitrate therapy is lower than that for enalapril, the additional cost for enalapril therapy could be justified by the additional number of lives saved. Sensitivity analysis on drug costs revealed that when the cost of enalapril therapy is 1.6 times the cost of hydralazine–isosorbide therapy, hydralazine–isosorbide therapy becomes inappropriately costly. Other economic analyses of the SOLVD study alone have, however, consistently demonstrated net cost savings for ACE inhibitor treatment as compared with standard therapy.

A socioeconomic analysis of the Munich Mild Heart Failure Trial (MHFT) has been performed, although the method used in the cost–effectiveness analysis was not provided. In the MHFT, 170 patients with mild CHF were treated with captopril (25 mg twice a day) or placebo, in addition to standard therapy (digitalis, digoxin, and nitrates, as appropriate). The primary result of this trial was a reduction in the occurrence of progressive CHF with captopril (from 30% to 12%). A total of 140 patients from this study were followed for a mean of 15 months to determine the effects of ACE inhibition on inpatient and outpatient total heart failure treatment costs. In this analysis, treatment was much more expensive in patients who developed progressive CHF, predominantly because of increased hospital charges (Figure 2). Despite the fact that ACE inhibitor therapy increased the cost of ambulatory drug treatment twofold, the effect of increased cost associated with progressive disease outweighed the higher treatment cost (Figure 3). It was concluded from MHFT that captopril therapy was cost–effective in the treatment of heart failure.

In a cost–consequence analysis of two recent clinical trials evaluating the effect of fosinopril on exercise tolerance and disease progression, we have shown that the expected savings with fosinopril in patients with heart failure was US$ 1,455,263 (calculated from Swiss francs 2,140,092 using a calculation factor of 0.68), or US$ 1,639,589 (Swiss francs 2,411,161) from the perspective of the Swiss third
party payers. In the cost–consequence analysis, a modified, or partial, cost–benefit analysis, which captures the short-term cost offsets by preventing complications or other sequelae due to treatment, of the study conducted by Brown et al,9 the use of fosinopril was associated with an overall cost saving per 1000 patients of US$ 1,639,589 (2,411,161 Swiss francs) per 6 months24 (Table 2). Hospitalizations are by far the most important factor in the costs of CHF and can account for over half of the total costs incurred in the management of these patients.25 When the Fosinopril Efficacy/Safety Trial (FEST)8 was evaluated, hospitalization, the most costly component of heart failure care, was needed by more of the patients who did not receive fosinopril (118 patients compared with only 26 in the treated group). Consequently, the costs per 1000 patients were considerably reduced by treatment with fosinopril26 (a saving of US$ 1,455,263 [2,140,092 Swiss francs] per 3 months) (Table 2).

Despite the fact that ACE inhibitors have been shown to improve symptoms, reduce the incidence of clinical events associated with disease worsening, and reduce hospitalizations, ACE inhibitors remain underused. Studies performed in the UK26,27 have shown that only approximately 15% to 30% of heart failure patients in general practice were being treated with

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### TABLE 2. COST–CONSEQUENCE ANALYSIS OF FOSINOPRIL WITHOUT DIGITALIS IN MILD TO MODERATE HEART FAILURE

<table>
<thead>
<tr>
<th></th>
<th>Without Fosinopril (n = 1000)</th>
<th>With Fosinopril (n = 1000)</th>
<th>Difference</th>
<th>Cost Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for additional diuretics or ICU†</td>
<td>392</td>
<td>267</td>
<td>125</td>
<td>1,148,987</td>
</tr>
<tr>
<td>Hospitalization for CHF‡</td>
<td>96</td>
<td>52</td>
<td>44</td>
<td>659,287</td>
</tr>
<tr>
<td>Development of severe CHF**</td>
<td>320</td>
<td>138</td>
<td>182</td>
<td>57,177</td>
</tr>
<tr>
<td>Fosinopril for 6 months††</td>
<td>—</td>
<td>1000</td>
<td>1000</td>
<td>225,862</td>
</tr>
<tr>
<td>Total cost savings:</td>
<td></td>
<td></td>
<td></td>
<td>1,639,589</td>
</tr>
</tbody>
</table>

* US$/1000 patients/6 months (calculated from Swiss francs using a conversion factor of 0.68).
† Calculated as either/or 2 days ICU at US$ 1,700 (2,500 Swiss francs) or 22.6 days of hospitalization at US$ 663 (975 Swiss francs).
‡ 22.6 days at US$ 663 (975 Swiss francs).
** US$ 314 (462 Swiss francs) for one GP visit then referral for one cardiologist visit followed by two GP follow-up visits and two laboratory examinations.
†† Fosinopril 20 mg once daily for 6 months = US$ 225.86 (332.15 Swiss francs).

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![FIGURE 4. Impact of the underuse of ACE inhibitors in CHF.](https://academic.oup.com/ajh/article-abstract/10/S7/272S/133738)
ACE inhibitors. In addition, ACE inhibitors have been demonstrated to be cost–effective and their cost is falling. There is therefore a true need to encourage increasing use of ACE inhibitors in patients with CHF, particularly in general practice, to provide cost–effective optimal treatment in health care systems with limited financial resources (Figure 4).

**THE LIMITATIONS OF PHARMACOECONOMICS**

Pharmacoeconomics will not answer all the substantive issues. For instance, the results of a study may not be conclusive enough to improve the quality of the decisionmaking. Or, the cost of gathering an extra piece of information may be greater than the extra benefit provided to the decisionmaker. For example, it is important that it is not only drug acquisition costs that are considered, as the side effect profile of a pharmacological treatment can impact on the total costs associated with management. In a study in hypertensive patients treated with ACE inhibitors, β-blockers, calcium channel blockers, and diuretics, the drug acquisition costs per year varied widely (approximately 300%) among drug classes. In contrast, when total costs of therapy were considered (including supplemental drug costs, laboratory monitoring, clinic visits, and treatment of side effects), there was much less variation between the different therapies (approximately 60%). Therefore, agents that are associated with a better side effect profile and that necessitate fewer physician visits are more cost–effective compared with those with a similar efficacy profile but are less well tolerated. Cough is considered to be an adverse effect particularly associated with ACE inhibitors; however, fosinopril, a unique ACE inhibitor with dual compensatory routes of elimination, has been shown to reduce the occurrence of ACE inhibitor–induced cough compared with enalapril. In addition, due to its compensatory route of elimination, fosinopril does not normally require dose adjustment in patients with renal impairment, a comorbid condition that often occurs in CHF patients and therefore may be associated with fewer physician visits. Consequently, physicians might expect that, in their patients with CHF, initiating fosinopril therapy may provide additional cost–benefits over other ACE inhibitors due to its improved side effect profile and particularly its simplified dosing regimen.

It is also important to be aware that health care cannot be rationed based on a simple economic calculation. There are always moral and ethical issues for society to take into consideration. There is also a political danger associated with economic evaluations, and they may become the “fourth hurdle” for the registration of new products. Regulators may not only review data about a product’s efficacy, safety, and quality, but may also demand economic data. This is the case in Australia and the Canadian province of Ontario, where reimbursement and decisionmaking are based on submitted pharmacoeconomic data.

There are, however, practical problems related to the introduction of a statutory requirement for economic appraisals. These economic assessments may delay patient access to new technologies. Because pharmacoeconomic studies are expensive and time-consuming, they may also increase the costs of developing and marketing a new product. Furthermore, analysis of results may be challenged, because there are no “gold standards” for conducting economic trials and many regulatory bodies do not, as yet, have the expertise to properly review and interpret the economic data. Nonetheless, many countries are moving toward statutory requirements for economic evaluations of new health care products prior to their release into the marketplace.

**PRESENT AND FUTURE NEEDS FOR ACTION**

Technological change in health care today is extremely rapid and is likely to continue to accelerate. Society now demands that all new products and services be clinically effective (in combating disease, reducing disability, and extending life), as well as cost–effective. However, the capacity to develop new technologies has far outstripped society’s ability to evaluate them and to make rational decisions about their appropriate use. In the absence of adequate assessments, suboptimal decisions are often made, which may result in the approval of ineffective new technologies that cause more harm than good.

If present circumstances continue, many older technologies will never be adequately assessed before they are replaced by new technologies. Decisionmakers will find themselves in a very difficult position regarding the purchase, adoption, insurance, and use of new technologies. Patients pressure physicians, and in turn physicians pressure administrators to purchase the latest innovations. Yet hospitals, insurers, funds set up for the sick, and the governments of many countries are under increasingly tight budget constraints. Thus, decisions concerning technology are almost made under pressure, especially as the information base is so inadequate.

Clearly, there is a vital need to produce authoritative information to assist the most important health care decisions. A strategy for health care technology assessment has four discrete, mutually reinforcing tasks: to be able to identify the technologies needing assessment, to collect data on the selected technology, to synthesize the data collected, and to disseminate all the information collected.

One of the great challenges that society faces is that a complete system for assessment would require the
monitoring of all health care technologies, both new and existing. Each technology should also be evaluated at various parts of its life cycle and the results summarized in a way that can be used by policy makers, health care providers, and the public.

REFERENCES