The Impact of Angiotensin-Converting Enzyme Inhibitors on Managed Care: Economic, Clinical, and Humanistic Outcomes

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Abstract

This article examines evidence of the improved clinical, economic, and humanistic outcomes associated with the use of angiotensin-converting enzyme inhibitors (ACEIs) in clinical practice, in particular in the areas of hypertension, diabetic nephropathies, post-myocardial infarction, and congestive heart failure. Pharmaco-dynamic and pharmacokinetic differences may exist among this class, however, these may not be clinically relevant when the drugs are given in equivalent doses. Although additional studies are necessary before a class effect can be assumed for each of these outcomes, it is important for clinicians to consider all of these outcomes when using ACEIs.

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Hypertension (HTN), one of the most common chronic conditions in the United States, is a predominantly asymptomatic disease in its early stages. Not treated or undertreated, HTN can result in long-term health consequences. The major adverse events associated with this condition include stroke, cardiac failure, and end-stage renal disease (ESRD).[1] Cardiovascular disease and stroke rank among the top 3 causes of death in the United States and account for an estimated economic burden of more than $259 million.[2] A positive relationship between elevated systolic and diastolic blood pressures (DBP) and cardiovascular risk is well established.[3] The objective of diagnosing and treating HTN is not only to lower blood pressure but also to reduce the risk of cardiovascular disease and the associated morbidity and mortality.

Congestive heart failure (CHF) is a common condition that is often defined as an inability of the heart to maintain sufficient blood flow to meet the body's metabolic needs. More than 2 million Americans have CHF and approximately 400,000 new cases are diagnosed each year.[4] Rates of morbidity and mortality for those with CHF are high, and its prevalence and incidence increase with age. CHF is the leading cause of hospitalization in older Americans, and the average 5-year mortality is estimated to be 50%. In the United States, the economic burden of treating CHF has been estimated to exceed $20 billion.[5]

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The prevalence of the disease results in a substantial economic burden.[6] Recently, newer and more expensive medications for the treatment of HTN have added to the direct medical cost of managing this disease. As a result, debate has arisen about the efficiency and effectiveness of treatment for HTN and the appropriate use of available medicines. However, drugs are only one component of the cost of treating HTN. Cost and consequences of various treatment approaches should be compared to outcomes to assess the most efficient and effective treatment regimen.

Given the economic and clinical burden of HTN and CHF and the potential to improve patient and population outcomes, the treatment and management of these chronic conditions are particularly amenable to the principles of managed care.[7] In the managed care setting, there are numerous opportunities to implement treatment guidelines, reduce treatment variability, encourage lifestyle modifications, and institute disease management programs.

Faced with an increase in pharmaceutical costs and in the overall cost of healthcare, payers and providers are questioning such expenses and their value, with value defined as the cost of care and the consequences of treatment. Medical, ethical, and social concerns about cost, access, and quality are motivating the healthcare community to consider a more comprehensive and value-based model of medical decision making. The value of a medication or treatment regimen should be based on its contributions to economic, clinical, and humanistic outcomes (ECHO).[8] Economic outcomes reflect the balance between cost and consequences of treatment. Clinical outcomes encompass the medical consequences of treatment, such as the treatment of HTN to prevent cardiovascular complications. Humanistic outcomes reflect the effect of the disease and its treatment on patients' quality of life, satisfaction with care, and well-being.

The purpose of this paper is to review the role of angiotensin-converting enzyme inhibitors (ACEIs) in the management of HTN, heart failure, and following myocardial infarction (MI), with a focus on economic and humanistic outcomes. ACEIs, beta-blockers (BBs), and diuretics are among the classes of drugs recommended as first-line treatment for HTN. Although the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) guidelines recommend diuretics and BBs for uncomplicated HTN, they further recommend ACEIs as the initial drug choice in specific situations such as HTN in diabetes with proteinuria or in CHF.[9] The circumstances, if any, under which one ACEI offers an advantage over relevant alternatives must be understood. Pharmacoeconomics can assist in the selecting of the treatment regimen.

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Clinical Outcomes of Angiotensin-Converting Enzyme Inhibitors

Significant clinical advantages of a drug generally dominate economic and humanistic considerations. In some cases however, the cost differences between treatments may be substantial and will then dominate the decision making.

Clinical outcomes are the medical events that occur as the result of a

disease or its treatment. Typical examples of clinical outcomes include mortality, years of life saved (YLS), number of strokes avoided, or days of dialysis saved. In some pharmacoeconomic evaluations, clinical endpoints, which are surrogate markers for the true outcome of interest, are used rather than outcomes. For example, in HTN, blood pressure is measured as a clinical endpoint or surrogate outcome, with lowering blood pressure becoming the primary focus of treatment. However, reduction in blood pressure is not the desired outcome of treatment; reductions in mortality, stroke, and ESRD are the treatment intentions. Although clinical endpoints are important because they often provide a scientifically valid and reliable indicator of the longer-term outcome measure, their use in economic evaluations of therapeutic interventions can be deceptive if short-term changes in endpoints do not reflect changes in the true outcome of interest. For example, a cost-effectiveness analysis may favor the use of a very inexpensive therapy because the therapy marginally improves the endpoint or outcome of interest.

Current literature provides an excellent review of the clinical characteristics of the ACEIs.[10-12] Clinically, the ACEIs vary in potency and pharmacokinetics. Specific ACEIs require a higher dose to achieve the same therapeutic response as others. Their efficacy, however, in HTN and heart failure appears to be a class effect. In antihypertensive capacity of the ACEIs when dosed and used appropriately, there does not appear to be any significant differences.

The pharmacokinetic differences of the ACEIs may provide rationale for preferring one or more agents as opposed to another. For example, captopril or lisinopril may be preferred for patients with extensive liver damage because these agents do not need to be metabolized to exert their pharmacologic effect, or clinicians may favor an agent such as fosinopril for patients with renal dysfunction because it may be eliminated hepatically. Some clinicians, however, may take advantage of an extended pharmacologic effect in this patient population by decreasing the dose of other ACEIs or extending the dosage interval.[13]

The absorption of the ACEIs is highly variable, but the clinical significance of this variability is not clear. The majority of ACEIs do not participate in drug-food interactions, with the exception of captopril and moexipril in which such an interaction may decrease the rate of drug absorption by 50%; the extent of absorption (area under the curve) is not as affected. Given this possibility, captopril and moexipril should be taken 1 hour before or after meals.[10,11] Absorption and metabolism of the ACEIs are decreased in patients with CHF resulting in a delayed onset of action. The need for dosage adjustment in these cases is unclear.[14,15]

Duration of action is an important clinical consideration in selecting an antihypertensive medication. Frequency of administration affects medication compliance, which in turn can affect clinical outcome. Formulations that can be dosed once daily are likely to improve patient adherence to therapy. With the exception of captopril, all of the oral ACEIs can be dosed once daily for the treatment of HTN. Trough-to-peak ratios are used by the US Food and Drug Administration (FDA) as a measure of antihypertensive effect. To be classified as an effective antihypertensive, the trough effect should be at least one-half the peak effect of the drug. According to a study by Leonetti and Cuspidi,[12] when the trough-to-peak ratio is greater than 50%, blood pressure is reduced in a smooth, constant manner. If the ratio is less than 50%, blood pressure reduction is more profound

and highly variable. Using this criterion, lisinopril, enalapril, and trandolapril, which have trough-to-peak ratios in this higher range, should provide a more stable blood pressure control than the other ACEIs.[16]

That ACEIs improve survival and reduce left ventricular hypertrophy in patients with CHF is well established. Using a meta-analysis of 32 clinical trials of ACEIs for CHF, Garg and Yusuf[17] suggested that reductions in mortality and improvements in cardiac function are probably class effects. Other studies also have provided support for the use of ACEIs in CHF treatment and their beneficial effects on survival.[18-20] In treating CHF, clinicians should attempt to titrate ACEIs to doses that have affected reduced mortality in clinical trials.

ACEIs have a positive clinical benefit in prevention of diabetic-related nephropathies. They reduce proteinuria and preserve glomerular filtration rates in patients with diabetes mellitus. These effects do not appear to depend on the blood pressure-lowering capacity of the agents, suggesting an independent renal protective effect for the ACEIs.[21-23]

The renal protective effects (decreased proteinuria and loss of renal function) of the ACEIs are independent of reduction in blood pressure. Support for this assertion is provided by a recent Italian study[24] in which benazepril was shown to be effective in slowing the rate of progression of heart failure and improving renal function survival in patients with diabetic nephropathy and in those with renal disease of various origins. Although studies have predominantly evaluated only benazepril, captopril, and enalapril in this area, renal protective effects appear to be common to the ACEIs. Patients with renal impairment may require dosage adjustments or may benefit from selection of an ACEI with dual routes of elimination such as fosinopril or trandolapril.

The ACEIs have also been shown to reduce mortality after MI. This reduction may be related to a decreased risk of subsequent MI and ventricular arrhythmias, and prevention of sudden cardiac death.

A meta-analysis by Domanski and associates[25] examined results from 15 randomized trials involving ACEI use following MI. Outcomes included sudden cardiac death, all cardiac deaths, and total mortality. ACEI therapy was associated with between 17% to 20% reduced risk of each of these negative outcomes. Table 1 summarizes the clinical outcomes from the analysis.

Based on the clinical evidence, most of the benefits of ACEIs are common to this class. Although specific patients may benefit from a particular ACEI, in population terms, the choice of an ACEI may be more a function of

Table 1. Odds Ratios of Mortality Outcomes in a Meta-Analysis Comparing ACEI to Placebo

	Number of Events		
Clinical Outcome	**ACEI group (N = 7658)**	**Placebo group (N = 7446)**	**Odds Ratio (95% CI)**
Total mortality	1105	1251	0.83 (0.71 – 0.97)
Cardiovascular mortality	958	1096	0.82 (0.69 – 0.97)
Sudden cardiac death	407	493	0.80 (0.70 – 0.92)

ACEI: Angiotensin-converting enzyme inhibitor; CI: confidence interval.
Source: Adapted from Reference 25.

its economic and humanistic consequences than its clinical efficacy.

Economic Outcomes of Angiotensin-Converting Enzyme Inhibitors

Optimal treatment of chronic conditions requires the proper balance of risks, benefits, and cost. Cost-effectiveness and cost-utility analyses can provide valuable insight into this balance.

An economic evaluation of a pharmaceutical intervention should compare the cost and consequences (outcomes) of 2 or more relevant treatments to determine which one produces the desired outcome at the least cost, thereby resulting in the most efficient treatment. Such an evaluation includes the following costs: direct medical, direct nonmedical, and indirect. Direct medical costs comprise the expenses associated with the "production" of care such as drugs, physician visits, and hospital care. Direct nonmedical costs include those activities that facilitate or support care but are not part of the basic medical care process, such as transportation and custodial care. Indirect costs reflect the effect a disease and its treatment have on patient productivity and are usually measured as lost wages or days of work missed. These same variables may also be evaluated as benefits if treatment is shown to decrease cost or improve productivity.

Significant clinical outcomes and endpoints, such as therapeutic efficacy, reduced mortality, and decreased morbidity, are important in estimating the economic outcomes of HTN treatment. Such clinical outcomes are balanced against treatment costs, and an economic ratio of cost per outcome is calculated. A cost-effectiveness methodology is often applied. This approach compares the cost of producing a health or medical outcome among 2 or more treatment alternatives that all achieve the desired outcome but may do so at differing levels of effectiveness. This can be seen with HTN and CHF in which the economic endpoints and outcomes, such as cost per mm Hg reduction in blood pressure, cost per YLS, or cost per quality-adjusted life year (QALY), have been computed. These outcomes are compared to determine which therapeutic alternative is the most efficient. If clinical outcomes are proven equal, a cost-minimization methodology can be applied to determine the least costly treatment alternative.[26,27]

This section will focus on pharmacoeconomic evaluations of ACEIs that use cost per YLS or QALY as economic outcomes. Studies that use a cost per clinical endpoint, such as cost per mm Hg of blood pressure reduced, will not be emphasized. Given variations in study design and relative effectiveness of treatments, comparison of studies using this type of economic outcome is very difficult.

Hypertension. Treatment of moderate-to-severe HTN has been proven beneficial and cost effective.[28] However, treating mild-to-moderate HTN has not been proved as cost effective when effectiveness is balanced against risks and benefits of treatment for such patients.[29] Economic evaluations of treatment alternatives can be instructive when this type of treatment uncertainty exits.

Data from the Hypertension Optimal Treatment (HOT) study[30] were used to estimate the cost effectiveness of antihypertensive therapy with felodipine, ACEIs, BBs, and diuretics. Of interest was the cost effectiveness of treating to 3 different target DBPs, 90, 85, and 80 mm Hg. The efficiency of adding aspirin to the regimen as a preventive measure for MI was also evaluated. The overall annual cost of managing HTN ranged from about $1200 for less aggressive treatment to $1400 for intensive treatment. The cost-effectiveness ratios were most favorable for treating

from "no blood pressure control" to a DBP of 90 mm Hg or less and for aspirin adjunctively ($4262 and $12,710 per life year gained). Further incremental reductions in DBP reduced the efficiency of treatment substantially. Reducing DBP from 90 to 85 mm Hg cost $86,360 per year of life gained, while a further reduction from 85 to 80 mm Hg increased the ratio to $658,370 per YLS. The authors concluded that treating to a diastolic target of 90 mm Hg and adding aspirin to the regimen were both cost-effective strategies in the management of HTN.

In a study by Stason and Weinstein,[31] a cost-effectiveness analysis was used to assess the efficiency of resource use in HTN treatment. Risk functions from the Framingham Heart Study were used to model the relationship between individual risk factors and the risk of mortality and morbidity from HTN. Variations in treatment response because of age, medication adherence, and duration of therapy were included in the model. To account for variations in health benefits from treatments, "fraction of benefit" (FOB) was assumed to range from full benefit to an age-varying partial benefit. FOB represented the proportional reduction in cardiovascular event risk associated with a reduction in blood pressure. It was assumed to decrease with increasing age at initiation of therapy, decrease with duration of therapy, and vary between mortality, stroke, and MI. Health benefits or outcomes were measured as YLS and adjusted for quality differences due to stroke, MI, and treatment side effects.

Treatment cost effectiveness was greater when pretreatment DBPs were higher. The cost per QALY gained was about twice as high for mild HTN treatment (DBP of 90 to 104 mm Hg) compared to moderate-to-severe HTN (DBP 105 mm Hg and higher). Cost effectiveness of treatment was found to vary with age and gender (Table 2); the ratios decreased with age for men and increased with age for women, suggesting age-related limits for HTN treatment. The researchers suggested that gender differences in cost-effectiveness ratios are explained by morbid events, such as MI and stroke, occurring later in life for women than men. In a study by Stevens and associates,[32] a decrease in cost effectiveness of HTN treatment with age for both men and women was reported. Estimates of cost effectiveness were very sensitive to the extent of actual blood pressure control and the degree to which excess risk of cardiovascular events were reduced.

A study evaluating the influence of age and gender on the efficiency of HTN treatment suggested that it is generally cost effective to treat men and women middle-aged and older, who have a diastolic pressure of 90 mm Hg or higher.[33] ACEIs and calcium channel blockers were found to be cost effective for patients at high risk for coronary disease, provided

Table 2. Cost Effectiveness of Hypertension Treatment (Cost Per QALY)

		Age (years)		
	Initial DBP (mm Hg)	20	40	60
Male	100	$ 5500	$ 8700	$50,100
	110	$ 3300	$ 5700	$16,300
Female	100	$14,700	$10,000	$ 8000
	110	$ 8500	$ 6100	$ 5000

QALY: Quality-adjusted life year; DBP: diastolic blood pressure.
Source: Adapted from Reference 31.

such patients receive the epidemiological expected reduction in risk for cardiovascular morbidity.

The influence of medication adherence on relative cost effectiveness of HTN treatment is noteworthy. Under an assumption of full adherence, the average cost effectiveness of treating patients with a DBP of 105 mm Hg or higher was $4850/QALY. When the full adherence assumption was relaxed, the cost per QALY increased to $10,500. For treating HTN in patients with DBP between 95 and 104 mm Hg, the ratios were $9880/QALY and $20,400/QALY, respectively.[8]

A cost-effectiveness analysis published in 1990[34] compared antihypertensive drugs from 5 therapeutic categories: propanolol (BB), hydrochlorothiazide (diuretic), nifedipine (calcium channel blocker), prazosin (alpha-adrenergic antagonist), and captopril (ACEI). A meta-analysis of 153 clinical trials was conducted to estimate drug dose, change in DBP, and change in serum cholesterol. The coronary heart disease policy model, developed by Weinstein and associates,[35] was used to simulate the effects of HTN treatment with each of the 5 drugs over 20 years for patients age 35 to 65 years with a DBP of 95 mm Hg or higher. The net cost of therapy for each year of the simulation was calculated by subtracting savings resulting from a lower incidence of coronary heart disease from the cost of drugs, physician visits, and laboratory procedures. The cost-effectiveness ratio for each drug was calculated by dividing the net present value of treatment cost by the present value of years of life gained with an economic outcome of cost per YLS. Cost-effectiveness ratios per YLS were as follows: propanolol, $10,900; hydrochloro-thiazide, $16,400; nifedipine, $31,600; prazosin, $61,900; and captopril, $72,100. The authors note, however, that the effectiveness and cost effectiveness of antihypertensive drugs are extremely sensitive to the drug's impact on quality of life.

In a study[36] that calculated cost-effectiveness ratios for diuretics, BBs, and ACEIs in the treatment of mild-to-moderate HTN (DBP of 90 to 114 mm Hg), treatment costs were assumed to be life-long and included initial diagnosis, drugs, laboratory tests, and follow up. Reductions in all-cause mortality and stroke incidence from treatment were estimated using risk functions from the Framingham Heart Study. The 3 drug classes were assumed to be equally effective in reducing the risk of HTN-related mortality and morbidity. Data were analyzed by gender, age, and DBP categories. A sensitivity analysis was used to assess variations in cost, risk reductions, and possible differences in side-effect profiles among the 3 therapeutic categories. For patients who had a positive gain in quality of life, average cost-effectiveness ratios (measured in Pound Sterling, GBP) for treating mild-to-moderate HTN across all age groups varied from 11,100 to 63,800 GBP for men and 22,100 to 195,000 GBP for women.

Gender and age were important factors influencing cost-effectiveness ratios in the study as well. Treating HTN in males and those patients with higher pretreatment DBPs was relatively more cost effective than treating HTN in females. It was also more cost effective to treat patients in the 45- to 64-year age range than those in the less than 45-year age groups. Under the assumption that quality of life was equal for the drug classes (eg, no difference in side-effect profiles), cost-effectiveness ratios favored treatment with diuretics and BBs. Under the assumption that ACEIs affect a slightly higher quality-of-life benefit (ie, fewer side effects) than diuretics and BBs, the cost-effectiveness ratios were more favorable for treatment with ACEIs (Table 3). Based on their findings, the researchers concluded

that diuretics were the most cost-effective therapeutic class and that drug treatment be used only when diastolic pressure was greater than 100 mm Hg. Results were highly sensitive to variations in the quality-of-life assumption.

A study by Briscoe and Dearing[37] reported cost savings from substitution within the class of ACEIs. In 1993, the pharmacy department provided an information intervention to physicians regarding the cost and comparability of enalapril, benazepril, and captopril, with a recommendation that patients be switched from enalapril to the lower cost product, benazepril. Prior to making a switch recommendation, a pharmacist reviewed the medical record to determine the appropriateness of the switch. The potential cost avoided by switching to benazepril was estimated from a review of a random sample of 104 medical records of the 1500 patients who were switched. Costs included medication switch expenses, changes in the number of clinic visits, changes in laboratory cost, and pharmacist time. Pre- and post-switch diastolic pressures were comparable, and 2-year net savings were estimated to be $259,054. The authors concluded that a program in which physicians voluntarily switched hypertensive patients from enalapril to benazepril reduced cost without compromising patient care.

Hilleman and associates[38] evaluated the cost of treating patients with newly diagnosed mild-to-moderate HTN (DBP > 95 to < 110 mm Hg) with 6 therapeutic classes of drugs: diuret-

Table 3. Cost-Effectiveness Ratios by Therapeutic Category and Patient Characteristics ($/QALY)

Age (years)	Initial DBP (mm Hg)	Cost-Effectiveness Ratio ($/QALY) by Gender: Male	Female
Diuretic Therapy			
50	110	$3856	$7472
60	90	$11,466	$26,790
Beta-Blocker Therapy			
50	110	$13,841	$27,252
60	90	$39,926	$100,840
ACEI Therapy*			
50	110	$22,401	$44,596
60	90	$64,323	$165,733
ACEI Therapy†			
50	110	$16,646	$26,142
60	90	$32,667	$45,892

DBP: Diastolic blood pressure, QALY: quality-adjusted life year.
*Equal side-effect profile assumption, †improved side-effect profile assumption.
Source: Adapted from Reference 36.

ics, BBs, centrally acting alpha$_2$-agonists, alpha$_1$-adrenergic blockers, calcium channel blockers, and ACEIs. The study attempted to determine the comprehensive cost of treating mild-to-moderate diastolic HTN by assuming equivalent clinical outcomes among the therapeutic classes and applying a cost-minimization methodology in the analysis. Retrospective chart reviews were conducted to identify patients with newly diagnosed mild-to-moderate HTN during the period 1985 to 1992 at the Creighton University Medical Center. A total of 1297 patient charts were reviewed; 673 patients met the study criteria and were included in the analysis. Resource utilization included the direct cost of medications, laboratory testing, clinic visits, and side-effect treatment costs. Patients were followed and costs accumulated from the time of initial treatment until blood pressure was controlled. The authors reported wide variations in treatment costs within the 6 drug classes.

Comprehensive cost of antihypertensive therapy with the ACEIs was compared; mean treatment costs per drug class were $895 for BBs, $1043 for diuretics, $1165 for centrally-acting alpha$_2$-agonists, $1243 for ACEIs, $1288 for alpha$_1$-adrenergic blockers, and $1425 for calcium channel blockers. At the time of the study, total cost of treatment with the newer antihypertensive agents (benazepril, fosinopril, quinapril, and ramipril) was one-third to one-half the cost of treatment with the older ACEIs (captopril, enalapril, and lisinopril). However, as a class, ACEIs were more expensive in terms of comprehensive costs than diuretics, BBs, and centrally-acting alpha$_2$-agonists. The authors concluded that although drug acquisition cost is important, it is not the dominant determinant of overall therapy cost. Comprehensive cost of treatment, not acquisition cost, should be used to determine the most efficient treatment regimen.

Diabetic Nephropathy. Diabetic nephropathy, characterized by albuminuria, proteinuria, and gradually declining renal function, is a long-term complication of uncontrolled hyperglycemia. An estimated 40% of patients with diabetes mellitus will develop diabetic nephropathy, and most patients who develop proteinuria will progress to ESRD. This disease is a debilitating and expensive condition with significant economic and humanistic consequences.[39] One of the most important treatment considerations for patients with diabetic nephropathy is antihypertensive therapy. Although all antihypertensive agents probably offer some renoprotective effect, only the ACEIs have been shown to have beneficial effects in patients with microabluminuria. Treatment of diabetic nephropathy with ACEIs has been shown to delay progression of the disease to ESRD. The renoprotective effects of the ACEIs appear to be a class effect that is independent of their antihypertensive action.[40]

Garattini and associates[41] have estimated the economic impact of prescribing ACEIs to treat diabetic nephropathy by using a decision-analysis model based on clinical data[42] to calculate the cost effectiveness of captopril versus placebo in reducing time spent in dialysis. The outcome for the clinical trial was number of dialysis years avoided. Results of the cost-effectiveness analysis showed captopril to be less costly and more effective than placebo.

Congestive Heart Failure. The cost effectiveness of captopril in CHF was evaluated in the Survival and Ventricular Enlargement (SAVE) trial,[43] which was a randomized, double-blind, placebo-controlled trial involving 2231 patients with acute MI and left ventricular dysfunction (LVD) (ejection

fraction of 40% or less) but without overt symptoms of heart failure or myocardial ischemia. Patients were followed for an average of 42 months. Primary endpoints included all-cause mortality, cardiovascular morbidity, cardiovascular-related mortality, and hospitalization. In the captopril arm of the trial, all-cause mortality decreased by 19%, cardiovascular-related mortality by 21%, development of CHF by 22%, CHF requiring hospitalization by 22%, and recurrent MI by 25%.

Using data from the SAVE trial, Szucs[44] conducted a retrospective cost-effectiveness evaluation of captopril from the perspective of the German Statutory Insurance Fund. Costs in the captopril group were more than $2 million greater than those for the placebo group but these costs were partially offset by a savings of $1.6 million resulting from reductions in MI and LVD. The clinical benefit of captopril treatment was calculated to be 495 life years gained for a cost-effectiveness ratio of $1160/YLS. The author concluded that captopril was cost effective in treating patients with LVD after MI.

Tsevat and associates[45] used data from the SAVE trial in a decision-analytic model to calculate the incremental cost effectiveness of captopril versus placebo in patients between the age of 50 and 80 years. Analyses were conducted under 2 different assumptions using the duration of the cardiovascular benefit from captopril: persistent-benefit and limited-benefit. Under the persistent-benefit assumption, survival effects from captopril were assumed to continue longer than the 4-year period observed in the trial. Under the limited-benefit assumption, costs were assumed to accumulate after 4 years but not benefits. Using the persistent-benefit analysis, cost-effectiveness ratios for patients between age 60 and 80 years ranged inversely with age from $3700/QALY to $5600/QALY; the cost-effectiveness ratio for 50-year-old patients was $10,400/QALY. Under the limited-benefit assumption, cost-effectiveness ratios ranged between $3600 and $9000/QALY for the 60- to 80-year-old group, and $60,800/QALY for the 50-year-old patients. These ratios suggest that captopril not only reduces mortality and morbidity, but is also cost effective in patients with a prior MI and LVD. Thus, the extent of therapy cost effectiveness depends on the age of the patient and the degree of persistence of ACEI benefit over time.

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The Studies of Left Ventricular Dysfunction (SOLVD), conducted by the National Institutes of Health, was a multicenter, randomized, placebo-controlled, double-blind evaluation of enalapril in patients with overt CHF and ejection fractions of 35% or less.[46] Primary outcomes of SOLVD were mortality and hospitalizations. A total of 2569 patients receiving conventional treatment were randomized to either enalapril or placebo in addition to their conventional therapy for heart failure. Study patients were followed for an average of 41.4 months. Patients treated with enalapril had a 16% reduction in all-cause mortality, an 18% reduction in cardiovascular deaths, a 22% risk reduction in death because of progressive heart failure, and a 26% risk reduction in death or hospitalization because of CHF. The authors concluded that the addition of enalapril to conventional CHF ther-

apy significantly reduced mortality and hospitalization.

Glick and associates[47] used resource utilization data from the SOLVD trial to estimate the cost effectiveness of enalapril. Cost per QALY was calculated for enalapril versus placebo for both short-term (within trial) and long-term (lifetime) treatment scenarios. In the within-trial analysis, enalapril was dominant; treatment with enalapril was more effective and less costly than placebo. Enalapril therapy was estimated to save an average of $717 per patient compared to placebo during the trial period. When a lifetime-treatment scenario was assumed, enalapril had a favorable cost-effectiveness ratio of $115/QALY. Based on this analysis, enalapril is cost saving in the short term or cost effective in the long run for treating patients with symptomatic CHF. Using the SOLVD data, a study by Butler and Fletcher[48] also reported cost savings from enalapril therapy; $171 to $252 during a 4-year treatment period.

Post-Myocardial Infarction. According to guidelines jointly published by the American Heart Association and the American College of Cardiology[49] as well as those published by the North of England ACE-inhibitor Guideline Development Group,[50] ACEIs provide an important benefit when used in patients who have suffered an MI. The cost effectiveness of this therapy depends upon several factors, including choice of patients receiving ACEI therapy.

A recent study[51] of the economic impact of the use of ACEIs following MI examined incremental costs per life year gained based upon 3 different treatment scenarios. The first scenario examined high-risk patients, described as patients who exhibited signs and symptoms of heart failure following MI. Data for life years gained from this group were obtained by the Acute Infarction Ramipril Efficacy study.[52] The second scenario includes treatment of an intermediate risk patient, described from the SAVE study as a patient who has asymptomatic LVD following MI. The third scenario is based upon results of the Fourth International Study of Infarct Survival Collaborative Group and Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico studies,[53,54] in which all patients suffering an MI were initially treated with an ACEI. Patients within this scenario then could continue ACEI therapy if they had either asymptomatic LVD (as in the second scenario) or symptomatic CHF (as in the first scenario). Estimates of YLS for the second and third scenarios were obtained from the respective studies.

The authors estimated incremental cost-effectiveness ratios over 10 years. Costs associated with the gain in YLS include those connected with treatment with the ACEI as well as other direct healthcare costs as a result of longer patient survival. Because the cost of various ACEIs differ, the authors performed their calculations based upon a yearly cost of therapy of 150 GBP and performed sensitivity analyses.

The incremental costs per life year gained ranged from 1752 GBP for the high-risk scenario to 2962 GBP for the intermediate-risk scenario. In addition, initial treatment of all patients, such as was detailed in the third scenario, increased the ratio to between 2017 GBP and 3110 GBP. These calculations were very sensitive to the estimated annual cost of ACEI therapy. The authors concluded that therapy with an inexpensive ACEI in either high-risk patients or in patients as described in the third scenario is highly cost effective compared to many other treatments.

Humanistic Outcomes

Humanistic outcomes are the consequences of a disease and its treatment on patient functional status or

quality of life, including physical and social functioning, general health and well-being, and life satisfaction. As such, humanistic outcomes are important in treatment plans, especially in the management of chronic illness in which treatment is more palliative and preventive than curative and in which side effects of treatment may affect quality of life. Clinicians should remember that patients often use humanistic outcomes to evaluate the effectiveness and quality of care they receive.

In the pharmacotherapy of HTN, medication side effects are often more apparent to the patient than the signs or symptoms of disease or the medication's effect on blood pressure. With mild-to-moderate HTN, which is largely asymptomatic, quality of life is not substantially affected early in the progression of disease.[55] The goal when treating these patients is to decrease their long-term risk of mortality and morbidity by lowering their blood pressure without negatively impacting their quality of life. The effects of therapy on humanistic outcomes are important clinically because many drug therapies for HTN produce undesirable side effects such as dizziness, fatigue, and headache. A study by Bulpitt and Fletcher[56] suggests that symptomatic and psychological well-being, cognitive function, sleep, activity, and life satisfaction are important dimensions of quality of life that should be assessed for antihypertensive therapies. Adverse effects of medications are barriers to compliance that may reduce patient adherence to the regimen and thus mitigate the chance of achieving desired clinical and economic outcomes.[57] An estimated 30% to 50% of patients discontinue their prescribed medication regimen within 1 year of initiation, which often results in increased utilization and cost of drugs, physician visits, hospitalizations, and other healthcare services.

The following are several studies that evaluated the effects of ACEIs on quality of life. Croog and associates[58] evaluated the effect on quality of life when patients with HTN were treated with methyldopa, propanolol, and captopril. Patients treated with methyldopa (a centrally-acting antiadrenergic agent) and propanolol (a BB) reported a negative effect on many quality-of-life domains. These drugs induced the frequency and severity of pharmacologically expected side effects. However, quality-of-life scores for the captopril group improved from baseline for global measures of quality of life as well as for individual dimensions of quality of life.

Humanistic outcomes are the consequences of a disease and its treatment on patient functional status or quality of life, including physical and social functioning, general health and well-being, and life satisfaction.

McCorvey and associates[59] reported no significant adverse cognitive or functional effects with hydrochlorothiazide, enalapril, or propanolol compared to placebo. However, these findings are not very convincing because only 16 of 30 patients enrolled completed the study.

In a comparison of atenolol and enalapril, Blumenthal and associates[60] reported similar safety, efficacy, and quality-of-life profiles for both drugs when they were used in patients whose disease was not controlled by diuretics alone. Thirty patients were randomly assigned to these 2 drugs in combination with hydrochlorothiazide. Several quality-of-life instruments measuring anxiety,

depression, psychiatric symptoms, memory, and psychomotor function were administered at baseline and at 4 and 8 weeks of treatment. No significant differences in quality-of-life scores for the atenolol and enalapril groups were reported. The small sample size and subsequent lack of statistical power limit findings of this study. Debate continues on this issue as the above findings are consistent with those of Herrick and associates[61] but conflict with the earlier work of Croog and colleagues.

In a meta-analysis of studies by Beto and Bansal[62] on quality of life of patients with HTN before and during long-term drug therapy, comparable small improvements in overall quality of life were reported for ACEIs, BBs, calcium channel blockers, and diuretics. There were no differences in quality-of-life scores between baseline and treatment for centrally-acting alpha$_2$-agonists or vasodilators. In addition, no negative effects on overall quality of life were observed for any of the 6 drug categories included in the meta-analysis. All drug categories, except vasodilators, exhibited small improvements in the psychomotor quality-of-life construct. A small improvement in general well-being was reported for the ACEIs, with ACEIs, BBs, and diuretics having a minor effect on the mood construct.

In a comparison of captopril and enalapril,[63] no differences in clinical efficacy and safety were found; no differences were observed in blood pressure, frequency of withdrawal from the study, laboratory outcomes, or major side effects. However, captopril demonstrated significant improvement in quality of life when compared to enalapril. The captopril group had more favorable changes in global quality of life and general perceived health as well as in the vitality, sleep, and emotional control dimensions. Change in quality-of-life scores varied with baseline scores. For both captopril and enalapril, post-treatment quality-of-life scores for patients with low baseline scores remained stable or improved. Patients with higher quality-of-life scores at baseline remained stable with captopril but declined with enalapril. The correlation between the quality-of-life scales and measures of symptom distress and life events suggests that the differences in scores were clinically important.

In the Department of Veterans Affairs Cooperative Vasodilator-Heart Failure Trial, enalapril was shown to improve survival compared with hydralazine plus isosorbide dinitrate in males with CHF who were being treated with digoxin and diuretics.[64] However, in an evaluation of the effects of such therapy on quality of life, Rector and associates[65] found no evidence that either group had an improved quality of life subsequent to treatment. In fact, both treatment groups demonstrated deterioration in quality of life during the course of the study. Because the study design did not include a placebo arm, it is not possible to evaluate the drugs' effects on the rate of decline in quality of life that is typically experienced by patients with CHF. It is possible that either or both regimens slowed the decline as opposed to producing improvements in patient well-being.

Conclusion

Economic Savings. Treatment of HTN offers potential economic savings by avoiding some of the long-term costs of morbidity and mortality. The cost-effectiveness ratios examined in this article suggest that HTN treatment falls within the range of many other medical interventions routinely used in modern healthcare. However, when additional risk factors are included and patients who are at risk for cardiovascular complications are targeted, the treating of HTN patients becomes a very efficient strategy. Studies have also shown that prescribing an ACEI is an efficient

choice in the treatment of mild-to-moderate HTN in middle-age and older patients (age 45 and above) and especially in those patients with diabetes or CHF.

When selecting a particular regimen, product cost, patient adherence, and the system impact of the drug on the use of other healthcare services must be evaluated.

Quality of Life. Several studies have compared the quality-of-life effects of ACEIs with other antihypertensive drug classes in the treatment of HTN and CHF. Given their improved side-effect profile compared to older therapies, the ACEIs result in improved quality-of-life outcomes. Comparisons within the ACEI class suggest a favorable humanistic profile for the entire class. In general, long-term health-related quality of life in patients with heart failure who were treated with ACEIs showed small improvements or did not differ significantly from placebo. However, in short-term assessments, quality-of-life outcomes demonstrated some benefit to prescribing ACEIs in the treatment of CHF. The larger, multicenter trials suggest that ACEIs do not produce a negative impact on quality of life in patients with CHF and may actually improve certain dimensions of quality of life.[66] Variations in quality of life reported in the literature highlight the importance of this dimension of treatment and the need to consider its implications when evaluating therapeutic options.

Implications for Managed Care. Although pharmacotherapy for these conditions might appear expensive when viewed in isolation, appropriate treatment provides substantial benefits in terms of reduced mortality and morbidity. Thus, the appropriate use of ACEIs has significant clinical, economic, and humanistic implications for managed care. Sound HTN disease management strategies need to be developed that reflect that the choice of regimen is based on the unit cost of drug therapy and the drug's effect on total resource utilization and desired patient outcomes. Programs that target patients with HTN who are at risk for cardiovascular complications, encourage appropriate treatment, and motivate patient compliance with treatment guidelines are likely to be very cost-effective strategies and patient-friendly interventions. The same can be said for the use of ACEIs in CHF and diabetes.

Quality of life and patient satisfaction are becoming important competitive variables for managed care because choice of plan and provider is influenced by patient satisfaction with the plan's performance. Managed care is acknowledging that patients infrequently judge the effectiveness of their managed care plan on changes in their diastolic blood pressure but on the effect the treatment has on their physical functioning and social well-being. Patient satisfaction and quality of life are being incorporated as benchmarks of plan performance by accrediting bodies and payer groups.

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