Heart failure is the leading cause of hospitalization in adults older than 65 years, and it is currently the most costly cardiovascular disorder in the United States, with estimated annual expenditures in excess of $20 billion. Recent studies have shown that selected pharmacological agents, behavioral interventions, and surgical therapies are associated with improved clinical outcomes in patients with heart failure, but the cost implications of these diverse treatment modalities are not widely appreciated. In this review, a brief outline of cost-effectiveness analysis is provided, and current data on the cost-effectiveness of specific approaches to managing heart failure are discussed. Available evidence indicates that angiotensin converting enzyme inhibitors, other vasodilators, digoxin, carvedilol, multidisciplinary heart failure management teams, and heart transplantation are all cost-effective approaches to treating heart failure; moreover, some of these interventions may result in net cost savings.

Heart failure affects an estimated 4.9 million Americans, and approximately 400,000 new cases are diagnosed each year. In 1995, there were 872,000 hospital admissions attributed primarily to heart failure, and there were an additional 1.8 million admissions with heart failure as a secondary diagnosis. Approximately 80% of all heart failure admissions occur in individuals older than 65 years, and one fifth of all admissions in that age group have a primary or secondary diagnosis of heart failure. As a result, heart failure is the leading indication for hospitalization in older adults.

From 1980 through 1993, the number of physician office visits for heart failure increased by 71%, from 1.7 million to 2.9 million annually. In addition, more than 65,000 patients with heart failure receive home health care each year. Moreover, in 1995, heart failure was listed as the primary cause of death in more than 43,000 cases and as a contributory cause in an additional 220,000 cases, and more than 90% of heart failure deaths occurred in patients older than 65 years.

Because of its high prevalence and associated high medical resource consumption, heart failure is now the single most costly cardiovascular illness in the United States, with total costs for 1998 estimated at $20.2 billion. Remarkably, heart failure hospitalization costs in 1991 exceeded those for all cancers and all myocardial infarctions combined. Moreover, in contrast to recent declines in age-adjusted mortality rates from coronary heart disease and hypertensive cardiovascular disease, the incidence and prevalence of heart failure are increasing, largely owing to the aging of the population. As a result, the costs of caring for patients with heart failure are expected to escalate well into the 21st century.

For these reasons, the last 2 decades have witnessed a remarkable explosion in heart failure research, and many new therapeutic options are now available. In addition, there has been considerable interest in defining the costs associated with heart failure management and identifying those interventions that are most efficacious from both the clinical and cost perspectives. In this review, a brief discussion of cost-effectiveness analysis is provided, followed by a summary of currently available evidence.
data relevant to the costs of treating patients with heart failure.

COST-EFFECTIVENESS ANALYSIS

The goal of cost-effectiveness analysis is to estimate the monetary cost required to achieve a gain in health benefit. More specifically, cost-effectiveness analysis estimates the incremental cost required to improve a selected clinical outcome by 1 unit (eg, cost per year of life saved, cost per stroke prevented). The goal is not to define the greatest benefit at the lowest cost, since in most cases it will not be possible to achieve both simultaneously.

Calculating the cost-effectiveness ratio requires estimating the change in cost associated with a given intervention (ie, the numerator of the ratio), as well as the change in health benefit provided by that intervention (ie, the denominator of the ratio). The notion of incremental costs and incremental benefits is crucial for cost-effectiveness analysis. Thus, the question posed is often of the form: “What is the monetary cost of moving from intervention X to intervention Y in relation to the associated change in health benefit in moving from X to Y?”

In estimating the cost-effectiveness ratio, cost is typically measured in dollars. Health benefit, however, may be expressed in a variety of ways. In cost-benefit analysis, both the costs and benefits are expressed in monetary terms (ie, the cost outlay is compared with the monetary value of the benefits obtained). Because it is often difficult to place a monetary value on a clinical benefit (eg, how much is 1 year of life or 1 less stroke worth?), cost-benefit analysis is used infrequently in the medical arena. When a study measures health benefit in disease-specific terms (eg, strokes prevented), the method is referred to generically as cost-effectiveness analysis. Although measuring health benefit in disease-specific terms may be helpful in comparing interventions for a specific condition, it is less useful for comparing interventions across diseases. For example, it is un-

The term cost refers to the actual or true costs associated with providing a service. Unfortunately, the true costs are often difficult to determine, since they may include such diverse resources as personnel, space, equipment, depreciation, and shared goods (eg, electricity and telephone). For this reason, charges are often used as a surrogate for costs. However, charges do not necessarily reflect true costs in any consistent fashion. For example, the charge for performing a specific procedure is often fixed, whereas the cost is dependent on several factors, including procedure volume (ie, the cost per case is lower if 10 echocardiograms are performed per day than if only 1 is performed). In an effort to overcome this and other limitations, a cost-to-charge ratio is often calculated. This ratio is based on estimated true costs and charges at a given institution, and it is therefore facility-specific. On the other hand, in most cases the cost-to-charge ratio is not based on specific procedures or diagnoses, and for this reason it may not provide a valid method for estimating costs.

Another approach to estimating costs is through reimbursement or collections data. Under the Medicare Prospective Payment System, hospitals receive a predetermined amount of money for each hospitalization, and this amount is based primarily on the discharge diagnosis category (diagnosis related group [DRG]). The reimbursement schedule, which is designed to reflect average costs adjusted for region and comorbidity, provides a simple method for gauging hospitalization costs. Unfortunately, DRG reimbursement may not reflect actual costs at a given institution or for an individual patient.

Discounting

In performing cost-effectiveness analyses, it is often important to determine the time frame during which costs and benefits accrue, since the current value of benefits to be achieved in the future is less than the value of the same benefits achieved

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In performing cost-effectiveness analyses, it is often important to determine the time frame during which costs and benefits accrue, since the current value of benefits to be achieved in the future is less than the value of the same benefits achieved
today. Thus, an individual would be willing to pay more today to prevent a stroke tomorrow than to prevent a stroke 10 years from now. Cost-effectiveness analysis accounts for the time value of both money and health benefits by discounting future value, usually at a fixed rate (eg, 3%/year).\textsuperscript{9,10}

**Sensitivity Analysis**

In most cost-effectiveness analyses, a series of assumptions are made concerning both costs and outcomes. For example, the average cost of intervention X may be estimated at $10,000, the health benefit may be assumed to be the prevention of 1 stroke for each 50 patients treated, and the risk of major complications may be estimated at 2%. Not surprisingly, the calculated incremental cost-effectiveness ratio may vary considerably depending on the validity of the baseline assumptions. Sensitivity analysis assesses the impact on the cost-effectiveness ratio of varying the baseline assumptions across a range of clinically plausible values.\textsuperscript{9,10} Sensitivity analysis thus provides insight into the stability of the cost-effectiveness ratio, identifies those baseline assumptions that have the greatest impact on overall costs, and defines boundaries beyond which a specific intervention may no longer be cost-effective (eg, if the reduction in mortality is less than 10% or if the complication rate exceeds 5%).

**Interpretation of Cost-effectiveness Analyses**

In comparing 2 treatment strategies using cost-effectiveness analysis, 1 of 4 results may occur (Figure). The first situation (quadrant I) occurs when the new intervention is both more effective (eg, saves more lives, prevents more strokes) and less expensive than standard treatment. In this case, the new intervention may no longer be effective (eg, if the reduction in mortality is less than 10% or if the complication rate exceeds 5%).

The analysis is straightforward. Unfortunately, such dominance occurs infrequently in the clinical setting. The third possibility occurs when the intervention is less effective and also less costly (quadrant II). This possibility presents a dilemma, since there may be situations where the less effective and less expensive treatment is actually more cost-effective. Depending on resource availability, the less costly therapy may represent the best clinical option. The fourth possibility (quadrant IV) occurs when the new therapy is both more effective and more expensive (eg, tissue plasminogen activator compared with streptokinase for acute myocardial infarction). In this last situation, which occurs commonly, as well as in scenario 3, the cost-effectiveness ratio can provide guidance as to the relative merits of the 2 interventions. Specifically, the incremental cost-effectiveness ratio (dollars per year of life gained) or the incremental cost-utility ratio (dollars per QALY gained) expresses the relative efficiency of the 2 interventions in producing health benefits.

What constitutes a cost-effective intervention? Clearly, any new treatment that reduces costs without compromising efficacy is cost-saving and therefore cost-effective. Renal dialysis is a common benchmark used to assess the cost-effectiveness of interventions that are both more effective and more costly. Renal dialysis is estimated to cost approximately $40,000 per year of life gained. Alternatively, Goldman et al\textsuperscript{17} have suggested that an incremental cost-effectiveness ratio of less than $20,000 per QALY is very attractive, a ratio of $20,000 to $60,000 per QALY is acceptable, a ratio of $60,000 to $100,000 per QALY is higher than currently accepted standards, and a ratio in excess of $100,000 per QALY is unattractive. However, since the incremental cost-effectiveness ratio involves a tradeoff between dollars spent and health benefits gained, the ranges suggested by Goldman et al (or by any arbitrary set of thresholds used for decision making) reflect society’s current willingness to pay for a specific benefit, and these ranges are therefore a matter of public policy rather than a scientifically based assessment of true cost-effectiveness.

In evaluating the results of cost-effectiveness analysis, several additional factors should be considered. Did the analysis compare 2 potentially effective interventions, or was a single intervention compared with placebo? It is often easier to demonstrate cost-effectiveness when the new treatment is compared with no therapy. Was the analysis based on costs or charges? Because charges typically exceed costs, analyses based on charges will tend to overestimate the true cost-effectiveness ratio. Was the population studied representative of clinical practice? If the study sample was highly selected, the results of the analysis may not be applicable to the general population. What was the time horizon for the analysis? Although data are often available only for the near term, health benefits may be long-lasting, and this should be factored into the analysis. Were costs and health benefits appropriately discounted? If not, the true cost-effectiveness could be either overestimated or underestimated. How were the benefits measured, and was quality of life taken into consideration? Did the study evaluate all costs, or was it limited to direct costs or to an even smaller component of total costs (eg, hospitalization costs)? The nature of the cost analysis can have a profound effect on the study’s implications. For example, a new intervention may have a favorable effect on stroke survival without increasing hospital costs, and such an intervention would therefore appear to be cost-effective. However, if neurological func-
tion is not improved, and if survivors require prolonged rehabilitation and nursing home care, the overall cost-effectiveness of the intervention may be greatly compromised.

Limitations

Although cost-effectiveness analysis provides a useful tool for evaluating therapeutic strategies and developing treatment and reimbursement policies, certain methodological limitations must be recognized. First, well-designed randomized controlled trials with prospectively collected cost data that directly measure the effect of a specific intervention on an identified outcome are exceedingly uncommon. This lack of direct evidence mandates the use of sophisticated modeling techniques that often combine data from a variety of sources and rely on expert judgment to estimate clinical outcomes and related costs. These estimates, which are often based on a series of assumptions, may or may not accurately reflect true costs and benefits. Although sensitivity analysis provides a method for evaluating the robustness of the model, the quantitative outcome of the analysis may nonetheless communicate a level of precision that is unwarranted.

A second limitation relates to the generalizability of a specific analysis to routine clinical practice. Cost-effectiveness analyses are often based on data from clinical trials that may involve a highly selected patient population treated in a specific practice environment (eg, an academic medical center) for a fixed period. Clearly, the results of these analyses may not be directly applicable to other patient populations, practice settings, or time horizons. In addition, analysts may use different methods and assumptions in developing cost-effectiveness models, and these differences may substantially influence the results. For these reasons, care should be taken both in comparing the results of different cost-effectiveness analyses and in applying the results to clinical practice.

A third limitation concerns the inability to measure intangible costs and the related difficulty of accurately quantifying quality of life. Both of these factors may serve to limit the validity of cost-effectiveness analyses in general and cost-utility analyses in particular.

Despite these limitations, cost-effectiveness analysis offers a unique means to generate insights into the costs and benefits associated with therapeutic interventions, for which the outcomes are often complex, dynamic, and uncertain.

Clinical Implications

Cost-effectiveness analysis may be used to compare costs associated with selected interventions when total resources are limited. For example, in choosing between 2 new and unrelated programs, both of which would cost $100 000 per year to operate, policy makers would have an apparently easy choice if 1 program spent $20 000 per QALY gained, while the other spent $200 000 per QALY gained. Without a cost-utility analysis, the relative clinical merits of the 2 programs may be less apparent.

At the level of the individual practitioner, however, the situation is much more complex. Physicians are appropriately concerned with providing each individual patient with the best possible care. Although cost may come into play, it is not and should not be the overriding concern. It cannot be expected, for example, that physician A will voluntarily withhold treatment X from a given patient because of the theoretical concern that administering such treatment will mean that physician B will not be able to give treatment Y (ie, a more cost-effective therapy) to another patient.

Despite these difficulties, cost-effectiveness analysis is increasingly being used to guide policy and influence medical decision making. It is therefore appropriate for physicians to have a working knowledge of cost-effectiveness analysis and its pitfalls.

TREATMENT OPTIONS

Angiotensin Converting Enzyme Inhibitors

Angiotensin converting enzyme (ACE) inhibitors have become the cornerstone of therapy in patients with significant left ventricular systolic dysfunction, as evidenced by a left ventricular ejection fraction of less than 0.40 whether or not overt heart failure is present. As shown in Table 1, several studies have now examined the cost implications of ACE inhibitor therapy.

In 1994, Paul et al developed a decision-analytic model to evaluate the cost-effectiveness of enalapril maleate therapy and of the combination of hydralazine hydrochloride and isosorbide dinitrate in comparison with standard therapy with digoxin and diuretics. Direct costs were calculated as the sum of hospitalization costs and medication costs. Hospitalization costs were derived using a detailed cost-accounting procedure incorporating the cost-to-charge ratio, indirect costs, and the costs of ancillary services. The costs used in this analysis were thought to reflect actual costs incurred by the hospital. Using this method, the average cost per hospitalization was estimated as $67 500 in 1992 US dollars. Medication costs were determined by surveying 10 retail pharmacies and averaging the results. The average cost for enalapril maleate therapy (20 mg/d) was $939 per year, and the cost of hydralazine hydrochloride (300 mg/d) plus isosorbide dinitrate (160 mg/d) therapy was $437 per year (both in 1992 US dollars). Efficacy data for the 2 treatments were derived from the first and second Veterans Administration Heart Failure Trials and from the Studies of Left Ventricular Dysfunction treatment trial. The model assumed that treatment was continued for 10 years and that the beneficial effects were linear over time. Both costs and benefits were discounted at the rate of 5% per year. Sensitivity analysis was performed to examine the impact of variations in model assumptions on incremental cost-effectiveness.

In the base-case scenario (ie, prior to performing sensitivity analysis), the principal findings of the study were that, relative to standard therapy, the incremental cost-effectiveness ratio for enalapril therapy was $9700 per year of life saved, while the ratio for hydralazine-isosorbide therapy was $5600 per year of life saved. These estimates are well below the cost-
Butler and Fletcher estimated the costs associated with mortality with enalapril SOLVD: 16% reduction in mortality with enalapril, fewer HF admissions. The authors also adjusted for cost differences associated with death in or out of the hospital. Cost data were reported undiscounted as well as discounted at a rate of 5% per year, and extensive sensitivity analyses were performed.

Overall, the authors estimated that the average additional costs of enalapril therapy were $1892 over 4 years. These costs were offset by projected cost savings of $2063 to $2144 per patient as a result of fewer hospitalizations, yielding net savings of $171 to $252 per patient (ie, enalapril treatment dominated). In the sensitivity analysis, the worst-case scenario cost-effectiveness ratio was $21 737 per year of life saved. Thus, this analysis also supports the view that ACE inhibitor therapy is highly cost-effective; a similar analysis performed in the United Kingdom reached the same conclusions.

In the Munich Mild Heart Failure Trial, 170 patients with New York

Table 1. Cost-effectiveness of Pharmacological Agents for the Treatment of Heart Failure

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Data Extraction</th>
<th>Therapeutic Agent(s)</th>
<th>Clinical Outcomes</th>
<th>Cost Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butler and Fletcher, 1996</td>
<td>SOLVD</td>
<td>Enalapril</td>
<td>16% Mortality reduction, increased survival by 1.68-1.80 mo, decreased HF admissions</td>
<td>Net savings of $171-$252/patient treated with enalapril; worst-case scenario: $21 735/y of life saved</td>
<td>Assumptions: 4-y treatment period, $6224/HF admission, discount rate: 5%y</td>
</tr>
<tr>
<td>Kleber, 1994</td>
<td>Munich MHFT</td>
<td>Captopril</td>
<td>59% Reduction in HF progression</td>
<td>Total costs “almost identical” with captopril vs placebo</td>
<td>Modest increase in cost for stable patients, cost-saving for patients with progressive HF</td>
</tr>
<tr>
<td>Tsevat et al, 1995</td>
<td>SAVE</td>
<td>Captopril</td>
<td>19% Mortality reduction, 22% reduction in HF admissions, 25% reduction in MIs</td>
<td>Cost per QALY ranged from $60 800 to $3700 for patients aged 50-80 y if benefit ceased after 4 y</td>
<td>If benefit persists beyond 4 y, CE ratio improves in younger patients; sensitivity analysis: CE ratio always favorable for patients aged 60-80 y</td>
</tr>
<tr>
<td>Ward et al, 1995</td>
<td>PROVED RADIANCE</td>
<td>Digoxin</td>
<td>PROVED: 50% reduction in HF exacerbations, RADIANCE: 77% reduction in HF exacerbations</td>
<td>Continuation of digoxin therapy saved $338/patient</td>
<td>Withdrawal studies; sensitivity analysis: digoxin is cost-saving if incidence of toxic effects &lt; 33%/y</td>
</tr>
<tr>
<td>Delea et al, 1999</td>
<td>US Carvedilol Heart Failure Trials</td>
<td>Carvedilol</td>
<td>65% Mortality reduction, 27% reduction in CV admissions</td>
<td>Incremental cost-effectiveness ratio range: $12 800 to $29 500/life-year saved</td>
<td>Projected lifetime costs based on limited or sustained benefits of therapy</td>
</tr>
<tr>
<td>Marius-Nunez et al, 1996</td>
<td>Michael Reese Hospital, Chicago, Ill</td>
<td>Milrinone, dobutamine</td>
<td>55% Reduction in admissions, 72% reduction in hospital days</td>
<td>86% Reduction in inpatient expenditures</td>
<td>Not a formal cost analysis, effect on mortality unknown</td>
</tr>
</tbody>
</table>

*V-HeFT indicates Veterans Administration Heart Failure Trial; SOLVD, Studies of Left Ventricular Dysfunction treatment trial; HCl, hydrochloride; HF, heart failure; MHFT, Mild Heart Failure Trial; SAVE, Survival and Ventricular Enlargement trial; MIs, myocardial infarctions; QALY, quality-adjusted life year; CE, cost-effectiveness; PROVED, Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin trial; RADIANCE, Randomized Assessment of Digoxin and Inhibitors of Angiotensin Converting Enzyme trial; CV, cardiovascular; and ICU, intensive care unit.

effectiveness ratio of renal dialysis, and both fall within the attractive
costs associated with mortality with enalapril, fewer HF admissions. The authors also adjusted for cost differences associated with death in or out of the hospital. Cost data were reported undiscounted as well as discounted at a rate of 5% per year, and extensive sensitivity analyses were performed.

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In the Munich Mild Heart Failure Trial, 170 patients with New York
Heart Association class II status heart failure and a left ventricular ejection fraction fraction of 0.33 or less were randomized to receive captopril therapy (25 mg twice daily) or to receive placebo and were followed up for an average of 2.7 years. The study’s major finding was that the rate of heart failure progression was reduced from 30% in the control group to 12% in the captopril therapy group (P = .01). In a subgroup of 140 patients, the effects of captopril therapy on inpatient and outpatient costs for heart failure treatment were examined over a 15-month period. Among patients who did not experience progressive heart failure during follow-up, total costs were higher in patients who were treated with captopril than in those who received placebo (303 vs 218 Deutschmarks per patient per month), primarily as a result of the added cost of drug therapy. In contrast, captopril therapy was cost-saving (ie, dominant) in patients who developed progressive heart failure (643 vs 737 Deutschmarks per patient per month). When these data were extrapolated to the total population and trial period, total cost outlays were “almost identical” in the 2 treatment arms, and the investigators concluded that treatment with ACE inhibitors did not impose “a further economic burden.”

In another study, Tsevat et al used a decision-analytic model to evaluate the cost-effectiveness of captopril therapy in patients with a left ventricular ejection fraction less than 0.40 following acute myocardial infarction. Data on costs, health-related quality of life, and 4-year survival were obtained directly from the Survival and Ventricular Enlargement (SAVE) trial. Since there was an interaction between age and survival benefit in the SAVE trial (older patients obtained greater benefit), separate cost-effectiveness models were developed for patients aged 50, 60, 70, or 80 years at the time of presentation. In addition, separate models were constructed assuming that the benefits of captopril therapy persisted beyond 4 years, or that they were limited to the first 4 years of therapy. (In the SAVE study, Kaplan-Meier curves for cardiovascular mortality, recurrent myocardial infarction, and incident heart failure continued to diverge up to 4 years, but data beyond 4 years are unavailable.) To translate the survival benefits associated with captopril therapy into QALYs, utility rates were determined in a subgroup of 82 patients using the time trade-off method, and these data were extrapolated to the entire study population. Cost estimates were based on actual resource utilization, with the DRG reimbursement rate used to estimate hospital costs and the resource-based relative value system used to calculate physician fees. Medication costs were based on the wholesale acquisition cost with the addition of a monthly dispensing fee. Outpatient clinic costs were adjusted to reflect usual practice, and the costs of outpatient diagnostic tests were assumed to be equal in both groups. All costs were converted to 1991 US dollars and discounted at a rate of 5% per year. Sensitivity analysis was performed over a wide range of variance in the baseline assumptions.

The cost of captopril therapy was estimated at $631 per year. Costs for other cardiac medications and outpatient care were similar in the 2 groups. Hospitalization costs were lower with captopril therapy during both the first and second years of treatment ($5930 vs $8687 for the first year, $1958 vs $2298 for the second year). Utility rates were slightly but not significantly lower in the captopril therapy group (0.88 vs 0.89). In the baseline limited-benefit cost-utility model, the incremental cost per QALY ranged from $60,800 for patients aged 50 years to $3600 for patients aged 80 years. In the persistent-benefit model, the estimated cost per QALY ranged from $10,400 for patients aged 50 years to $3700 for patients aged 80 years. In the worst-case scenario sensitivity analysis, captopril therapy remained cost-effective for patients aged 60, 70, and 80 years ($29,200, $1,700, and $8700 per QALY, respectively), but was unattractive for patients aged 50 years ($217,600 per QALY).

In summary, multiple analyses have indicated that ACE inhibitor therapy in patients with left ventricular systolic dysfunction is almost always cost-effective and frequently cost-saving.

Other Pharmacological Agents

The recently completed Digitalis Investigation Group study found that digitalis reduced all-cause hospital admissions by 6% and reduced the composite end point of death or hospitalization caused by worsening heart failure by 25%. Unfortunately, no associated cost analysis has been published. However, Ward et al used a decision-analytic model to estimate the costs associated with withdrawal of digoxin therapy in patients with New York Heart Association class II or III status heart failure, an ejection fraction less than 0.35, and sinus rhythm (Table 1). Outcome data were derived from the Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin (PROVED) and the Randomized Assessment of Digoxin and Inhibitors of Angiotensin Converting Enzyme (RADIANCE) trials. In the PROVED trial, which enrolled patients not receiving concomitant ACE inhibitor therapy, the relative risk of developing an exacerbation of heart failure within 12 weeks of randomization was 0.50 in patients continuing to receive digoxin therapy compared with those from whom digoxin therapy was withdrawn. In the RADIANCE trial, which enrolled patients who were also receiving an ACE inhibitor, the relative risk of developing heart failure within 12 weeks was 0.23 in patients continuing to receive digoxin therapy compared with those no longer receiving treatment.

Cost estimates in the PROVED and RADIANCE trials were based on Health Care Finance Administration data and local practices using the cost-to-charge ratio; they included the costs of heart failure–related office visits, emergency department visits, and hospitalizations, as well as the costs of digoxin therapy, serum digoxin monitoring, and the costs of treating digoxin toxicity. All costs were converted to 1991 US dollars and a detailed sensitivity analysis was performed. Compared with digoxin therapy withdrawal, continuation of digoxin therapy was associated with a net annual cost savings of $338 per patient (range, 588-5685 per patient per year). In the sensitivity analysis, maintenance of digoxin
therapy was cost-saving as long as the annual incidence of digoxin toxicity was less than 33%. Projecting the results of this analysis to the estimated 1.2 million adults in the United States with stable heart failure, the authors estimated that digoxin therapy saves $406 million annually in total heart failure costs (range, $106-$822 million). Importantly, digoxin therapy was cost-saving both in patients treated with an ACE inhibitor and in those not taking an ACE inhibitor.

The principal limitation of this analysis relates to the overall design of the PROVED and RADIANCE trials, both of which were withdrawal studies. The implications of these findings for patients not previously treated with digoxin therapy are thus unclear. In addition, generalizing the findings to the larger US population is rather speculative. Nonetheless, since digoxin is an inexpensive therapy that significantly reduces both all-cause hospitalizations and heart failure hospitalizations, it is quite likely that digoxin therapy is cost-effective and possibly cost-saving. Clearly, the analysis from the PROVED and RADIANCE trials supports this hypothesis.

Three large, prospective, randomized studies have now demonstrated the beneficial effects of ß-adrenergic blocking agents for the treatment of heart failure, and a cost analysis based on data from the US Carvedilol Heart Failure Trials Program found that carvedilol therapy is also cost-effective (Table 1). Using a Markov model to project life expectancy and lifetime medical costs, the addition of carvedilol to conventional heart failure therapy was associated with an incremental cost-effectiveness ratio of $29,477 per life-year saved in a limited benefits scenario and $12,799 per life-year saved in an extended benefits model. In both of these models, the benefits of carvedilol therapy, in terms of reducing hospitalizations and mortality, were assumed to persist for 3 years after the end of the carvedilol therapy trial and then to either end abruptly (limited benefit) or taper gradually over a period of 3 years (extended benefit). Since the extended benefit scenario is more likely to reflect actual practice, it appears that carvedilol therapy is cost-effective, although probably not cost-saving.

An additional therapeutic option for patients with advanced heart failure is intermittent inotropic therapy. In a retrospective observational study, Marius-Nunez et al evaluated the effects of intermittent outpatient treatment with milrinone therapy (n = 32) or dobutamine therapy (n = 4) in patients with stable New York Heart Association class III or IV status heart failure (Table 1). Compared with the period prior to treatment, outpatient inotropic therapy was associated with a 55% reduction in hospital admissions, a 72% reduction in hospital days, and a 52% reduction in emergency department visits. Although a formal cost analysis was not performed, the authors estimated that intermittent inotropic therapy was associated with an 86% reduction in inpatient expenditures. This study is limited by its before-after design, the fact that certain patients were excluded from the analysis, the failure to account for the cost of outpatient therapy, and uncertainty about the long-term effects of inotropic therapy on clinical outcomes. Future studies that address these limitations may demonstrate that intermittent inotropic therapy is a cost-effective approach to treating a highly selected group of patients with end-stage heart failure.

Nonpharmacological Therapies

Heart failure often occurs in the setting of multiple comorbid illnesses, such as hypertension, coronary artery disease, diabetes mellitus, renal insufficiency, and chronic lung disease. In addition, heart failure management is often complicated by behavioral (eg, noncompliance), psychological (eg, depression), social (eg, isolation, especially in the elderly), and economic (eg, inability to pay for medications) factors, and these factors frequently contribute to heart failure exacerbations. For these reasons, many centers are now employing an interdisciplinary approach to heart failure management, and several studies have now documented improvements in clinical outcomes (Table 2). Although the composition of an interdisciplinary team may vary from center to center, the team is usually directed by a nurse-coordinator or case manager, with additional support provided by a diettitian, social worker, pharmacist, and/or home health specialist, in addition to the primary care physician and consultant cardiologist.

While all of the studies listed in the first section of Table 2 reported a favorable effect on clinical outcomes, only 4 reported cost data. In 1983, Cintron et al evaluated the effects of a nurse-practitioner-based clinic on hospital admissions, total hospital days, and medical costs in 15 patients with chronic heart failure. Data from an average period of 24 months prior to implementation of the clinic were compared with data for an equivalent period after implementation. Medical costs were calculated as the sum of total inpatient hospital days at $165 per diem plus total outpatient visits at $61 per visit. The inpatient per diem cost estimate was obtained from the hospital’s financial division; the outpatient visit costs reflected average costs for all services, including laboratory tests, medications, and transportation.

Prior to implementing the study intervention, the annual number of hospitalizations was 1.8 ± 0.2 per patient and total hospital days averaged 62 ± 14 per year (mean ± SD). Following the intervention, the annual number of hospitalizations declined 60% to 0.7 ± 0.2 per patient and hospital days fell by 85% to an average of 9 ± 4 per patient (P < .001 for both). As a result, average annual inpatient costs decreased by $8745 per patient. Patients averaged 18 outpatient clinic visits per year after intervention, resulting in an average increase in outpatient costs of $736 per patient. Thus, there was a net mean cost savings of $8009 per patient per year. Limitations of this study include the nonrandomized before-after study design and the very small number of patients. In addition, data on mortality and quality of life were not reported. Also, it is not clear whether the cost of the nurse-practitioner’s salary was included in the analysis. Nonetheless, the data clearly suggest that the intervention improved outcomes and reduced costs and was therefore dominant.
<table>
<thead>
<tr>
<th>Source, y</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Intervention</th>
<th>Duration of Follow-up</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cintron et al,38 1983</td>
<td>Observational preintervention and postintervention</td>
<td>15</td>
<td>Nurse-practitioner–based clinic with physician referral as needed, average of 18 clinic visits per year</td>
<td>24 mo†</td>
<td>61% Reduction in hospitalizations, 85% reduction in hospital days, cost reduction of $8000/patient per year</td>
<td>Mean age, 65 y; NYHA class III-IV; improved patient satisfaction</td>
</tr>
<tr>
<td>Rich et al,39 1993</td>
<td>Randomized pilot study</td>
<td>98</td>
<td>Nurse-directed team with patient education, dietary counseling, social services, home care, telephone follow-up</td>
<td>90 d</td>
<td>27% Reduction in readmissions, 25% reduction in hospital days</td>
<td>All patients aged &gt;70 y; mean NYHA class, 2.8</td>
</tr>
<tr>
<td>Lasater,40 1996</td>
<td>Observational preintervention and postintervention</td>
<td>80</td>
<td>Nurse-managed heart failure clinic with access to physician, dietitian, and social worker</td>
<td>6 mo</td>
<td>14% Reduction in hospitalizations; 22% reduction in length of stay, hospital costs reduced by $500/patient</td>
<td>No information provided on patient population</td>
</tr>
<tr>
<td>Kostis et al,41 1994</td>
<td>Randomized parallel groups</td>
<td>20</td>
<td>Exercise, cognitive therapy, stress management, dietary counseling</td>
<td>12 wk</td>
<td>Improved exercise tolerance; reduced anxiety, depression; enhanced weight loss</td>
<td>Age range, 54-77 y; digoxin group and placebo group as controls</td>
</tr>
<tr>
<td>Kornovski et al,42 1995</td>
<td>Observational preintervention and postintervention</td>
<td>42</td>
<td>Intensive home care surveillance by internist and paramedical team, at least 1 visit per week</td>
<td>1 y</td>
<td>62% Reduction in hospitalizations, 77% reduction in hospital days, 72% reduction in CV admissions, improved ability to perform activities of daily living</td>
<td>Mean age, 78 y; NYHA class III-IV</td>
</tr>
<tr>
<td>Rich et al,43 1995</td>
<td>Randomized clinical trial</td>
<td>282</td>
<td>Nurse-directed team with patient education, dietary counseling, social services, home care, telephone follow-up</td>
<td>90 d</td>
<td>44% Reduction in readmissions; 56% reduction in HF admissions, improved quality of life, improved compliance, cost reduction of $460/patient</td>
<td>Mean age, 79; high-risk population; benefits persisted up to 1 y</td>
</tr>
<tr>
<td>Stewart et al,44 1999</td>
<td>Randomized clinical trial</td>
<td>97</td>
<td>Single home visit by nurse and pharmacist 1 wk after discharge</td>
<td>18 mo</td>
<td>50% Reduction in admissions, 46% reduction in mortality, 52% reduction in hospital costs</td>
<td>Mean age, 75 y; NYHA class II-III; high risk population</td>
</tr>
<tr>
<td>Dennis et al,45 1996</td>
<td>Retrospective chart review</td>
<td>24</td>
<td>Home health nurse, teaching, clinical assessments</td>
<td>1 y</td>
<td>Frequency and intensity of visits inversely correlated with readmissions</td>
<td>Age, other demographic data not specified</td>
</tr>
<tr>
<td>Martens and Mellor,46 1997</td>
<td>Retrospective chart review</td>
<td>924</td>
<td>Home health nurse, teaching, clinical assessments</td>
<td>90 d</td>
<td>36% Fewer readmissions in patients receiving home care</td>
<td>Mean age, 71 y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Intervention</th>
<th>Duration of Follow-up</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>West et al,47 1997</td>
<td>Observational preintervention and postintervention</td>
<td>51</td>
<td>Physician-supervised, nurse-mediated, home-based system with frequent telephone contacts targeting medication dosing, compliance, activities, symptom status</td>
<td>138 ± 44 d‡</td>
<td>74% Reduction in hospitalizations; 87% reduction in HF admissions; fewer office and ED visits; improved symptoms, quality of life, exercise tolerance; improved ACE inhibitor dosing and salt restriction</td>
<td>Mean age, 66 y; NYHA class I-II, 60%, class III-IV, 40%; initial clinic visit, subsequent follow-up by telephone</td>
</tr>
<tr>
<td>Fonarow et al,48 1997</td>
<td>Observational preintervention and postintervention</td>
<td>214</td>
<td>Comprehensive management by HF/transplant team, including diet, exercise, teaching, medications</td>
<td>6 mo</td>
<td>35% Reduction in hospitalizations; improved NYHA class and exercise tolerance, improved medication dosing, cost reduction of $9800/patient</td>
<td>Mean age, 52 y; NYHA class III-IV</td>
</tr>
</tbody>
</table>

*NYHA indicates New York Heart Association; CV, cardiovascular; HF, heart failure; ED, emergency department; ACE, angiotensin-converting enzyme.
†Mean.
‡Mean ± SD.
In a second study, Lasater analyzed the effects of a nurse-managed heart failure clinic on hospital readmissions, length of stay, and hospital charges in 80 patients with chronic heart failure. In the 6-month period prior to starting the clinic, the hospital readmission rate was 25.6% and the average hospital length of stay was 7.3 days. During the 6 months after the clinic was started, the readmission rate declined to 21.9% and the average length of stay decreased to 5.7 days (P < .05 for both). Hospital charges were reduced from $6898 per patient before intervention to $6405 after intervention, for net savings of $493 per patient. This study is limited by its nonrandomized design as well as by its failure to account for the cost of the intervention. In addition, it is unknown to what extent the hospital charges reflected the actual costs. Despite these problems, the study lends support to the use of a nurse-based clinic as an effective and possibly cost-effective approach to heart failure management.

In the largest study published to date, Rich and colleagues randomized 282 patients 70 years of age or older who were hospitalized with heart failure to conventional, physician-directed care or to conventional care supplemented by a nurse-directed interdisciplinary team. The intervention included intensive patient education, dietary consultation, social service evaluation, medication review, and close follow-up after discharge by a home health specialist and study nurse. All patients were evaluated for 90 days, during which all-cause readmissions were reduced by 44% (P = .02), heart failure readmissions were reduced by 56% (P = .04), and the number of patients experiencing multiple readmissions was reduced by 61% (P = .01). Patients in the intervention group also experienced an improved quality of life and greater compliance with medications and diet than patients in the usual care group.

During the final year of the study (1994), the authors prospectively collected detailed cost data for 57 patients through the use of cost logs and frequent patient interviews. Cost data were analyzed in 4 domains, including readmission costs (based on DRG reimbursement), other direct medical costs (eg, outpatient services, medications), caregiver costs (ie, time spent by family and friends caring for the patient, prorated at $6/hour), and costs associated with the intervention itself. As shown in Table 3, the combined costs of the intervention, caregiver time, and other medical services were $598 higher per patient in the treatment group (P, not significant). Conversely, readmission costs per patient were $1058 lower in the treatment group (P = .03), yielding a net cost savings of $460 per patient. Thus, from the cost-effectiveness perspective, the intervention dominated. The principal limitations of this study were that the patient population was highly selected (only 21% of elderly patients with heart failure were enrolled), and the index event for all patients was acute heart failure exacerbation. The generalizability of these findings to other populations and to the outpatient setting is therefore unknown.

More recently, Stewart et al reported the results of a randomized trial involving 97 patients with heart failure with an average age of 75 years. Patients received usual care supplemented by the study intervention (n = 49), which included predischARGE teaching by a study nurse and a single home visit by a nurse and a pharmacist 1 week after discharge. The purpose of the home visit was to assess compliance and clinical status, and subsequent referrals were made to the primary care physician and a local pharmacist as needed. Patients were evaluated for 18 months, during which the intervention group experienced 50% fewer readmissions. Mean hospital costs per patient were 52% lower in this intervention group ($5100 vs $10 600 in Australian dollars), and the cost of the intervention was estimated at $190 per patient (Australian dollars).

In summary, although additional study is needed, currently available data strongly suggest that an interdisciplinary, nonpharmacological approach to heart failure management can be highly cost-effective, particularly in patients at higher risk who have multiple comorbid conditions and/or other barriers that may interfere with their ability to comply with treatment.

**Table 3. Cost of Multidisciplinary Heart Failure Management During 90 Days of Follow-up**

<table>
<thead>
<tr>
<th>Cost Domain</th>
<th>Control Group</th>
<th>Treatment Group</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>NA</td>
<td>216</td>
<td>+216</td>
</tr>
<tr>
<td>Caregivers</td>
<td>828</td>
<td>1164</td>
<td>+336</td>
</tr>
<tr>
<td>Other medical care</td>
<td>1211</td>
<td>1257</td>
<td>+46</td>
</tr>
<tr>
<td>Readmissions</td>
<td>3236</td>
<td>2178</td>
<td>−1058†</td>
</tr>
<tr>
<td>Total</td>
<td>5275</td>
<td>4815</td>
<td>−460</td>
</tr>
</tbody>
</table>

*Average cost per patient. NA indicates not applicable.
†P = .03.

**Multimodality Therapy**

Two recent studies used an interdisciplinary approach combining nonpharmacological measures with efforts to maximize medical therapy (Table 2). In the first study, West and colleagues evaluated 51 patients using a before-after study design and reported that a physician-supervised, nurse-mediated, home-based system for heart failure management was associated with a 74% reduction in hospital admissions and a 53% reduction in emergency department visits. Although no cost analysis was performed, the intervention costs were likely modest, and the management system was almost certainly cost-saving.

In the second report, Fonarow et al studied 214 patients referred for possible heart transplantation. Treatment included intensive patient education, optimization of the medication regimen, and close follow-up after the initial assessment. Compared with the 6-month period prior to referral, total hospital admissions were reduced by 33%...
therapeutic modalities improve clinical outcomes (including a reduction in hospital admissions), but they do so at incremental cost-effectiveness ratios that are well within the desirable range, and that, in some cases, provide a net cost savings. Within the limitations of cost-effectiveness methodology, these data indicate that the judicious use of medications, nonpharmacological interventions, and surgical procedures not only leads to the best clinical outcomes, but also provides the most cost-effective approach to heart failure care.

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REFERENCES