Cost-Effectiveness of Beta-Blocker Treatment in Heart Failure

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There is a growing economic burden from the treatment of heart failure that accounts for more than 5% of total health care expenditures. Hospitalization contributes between 60% and 75% of this total expense. The addition of ß-blockers to conventional heart failure therapy results in a significant reduction in hospitalization. As a consequence, ß-blocker therapy in heart failure is very cost-effective and compares favorably to that of other generally accepted medical interventions

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Heart failure has become an important health care problem within the United States. The incidence or number of new cases per year has grown steadily over the last two decades, and the American Heart Association estimates that there were 550,000 new cases in the year 2000.[1] The prevalence of heart failure increases with age. Approximately 1% of adults in their 50s have a diagnosis of heart failure, and 10% of 80-year-olds suffer from this syndrome. As a consequence of our aging population and the improved survival from acute coronary syndromes, there has been a dramatic growth in the number of individuals with heart failure.[2] There were approximately

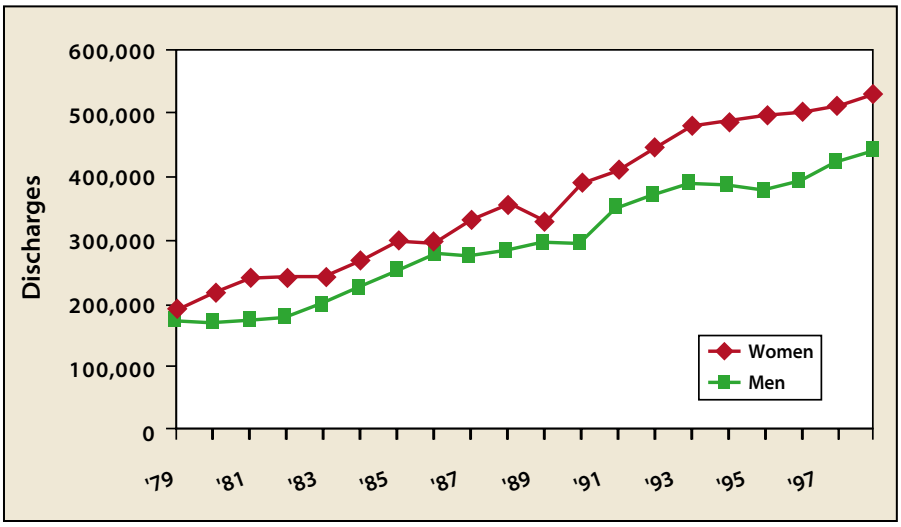

Figure 1. *Heart failure hospitalization for men and women in the United States from 1979 to 1999. The number of heart failure hospitalizations is increasing for both men and women. Source of data: Centers for Disease Control/National Center for Health Statistics and American Heart Association. Reproduced with permission, American Heart Association World Wide Web Site, www.americanheart.org. ©2002, Copyright American Heart Association.*

3.5 million patients with heart failure in 1991; this number grew to 4.7 million patients in 2000 and is expected to reach 10 million by the year 2037.[3] The fact that heart failure contributes to the death of about 260,000 patients yearly is further evidence of its significant impact on the lives of Americans.

The prevalence of heart failure increases with age.

With the growth of the number of individuals with heart failure, it is not surprising that the number of heart failure hospitalizations has also increased dramatically. It is estimated that heart failure was the primary admission diagnosis for 978,000 hospitalizations in the year 2000.[4] As can be seen in Figure 1, the number of heart failure hospitalizations has been steadily increasing for both men and women. Heart failure is now the most common primary admission diagnosis in patients older than 65 years.[2–4] Furthermore, patients with a previous hospitalization for heart failure are at even greater risk for recurrent hospitalization and death.[3,4]

The annual costs for caring for patients with heart failure is estimated to range from $10 billion to nearly $40 billion.[2] Heart failure now accounts for over 5% of total health care expenditures. Inpatient care contributes between 60% and 75% of this total expense.[2] Because an average admission to the hospital for heart failure costs over $10,000,[2] therapies that reduce the frequency of hospitalization represent a significant opportunity for cost savings. If we do not implement successful strategies to reduce hospitalization, the costs of therapy for heart failure will continue to climb.

Heart failure contributes to the death of about 260,000 patients yearly.

Effect of Beta-Blocker Therapy on Hospitalization

Several prospective, randomized, placebo-controlled trials have shown a reduction in hospitalization with the addition of β-blocker therapy to angiotensin-converting enzyme (ACE) inhibitors and diuretics with or without digitalis.[5–9] This review will discuss the results from the trials of carvedilol, a nonselective β-blocker with α_1-antagonist activity, and the β_1-selective β-blockers metoprolol succinate and bisoprolol. Although all three of these drugs have been shown to reduce mortality in patients with heart failure, currently only carvedilol (Coreg; GlaxoSmithKline, Research Triangle Park, NC) and metoprolol succinate (Toprol-XL, AstraZeneca, Waltham, MA) have been approved by the U.S. Food and Drug Administration for the treatment of heart failure.

Australia/New Zealand Trial

The Australia/New Zealand (ANZ) trial[5] studied 415 patients with a prior history of myocardial infarction, left ventricular ejection fraction below 0.40, and a history of heart failure symptoms. Background therapy included ACE inhibitors (unless proven intolerant) and diuretics. Therapy with digitalis was permitted but not mandated. This trial included many patients with mild symptoms, with 30% of subjects classified as New York Heart Association (NYHA) functional class I at the time of randomization. At 18 months of follow-up, the addition of carvedilol to standard therapy reduced the risk of death or hospitalization by 26%. Hospitalizations for any cause were observed in 58% of placebo

Table 1
Effects of Carvedilol on Hospitalizations

Cause of Hospitalization	Placebo (n = 389)		Carvedilol (n = 696)	
	Total	Per Patient	Total	Per Patient
All cause	160	0.40 ± 0.78	208	0.30 ± 0.78†
Cardiovascular	119	0.30 ± 0.69	143	0.21 ±0.57*
Worsening heart failure	61	0.15 ± 0.54	52	0.07 ± 0.34*

Data in per patient columns are mean plus or minus standard deviation.
* $P < .05$.
† $P < .01$.
Data from Fowler et al,[10] with permission.

subjects and 48% of carvedilol subjects, a 23% risk reduction ($P < .05$). Cardiovascular hospitalizations occurred in 40% of placebo subjects and 34% of carvedilol subjects, an 18% risk reduction that did not achieve statistical significance.

U.S. Carvedilol Trials Program

The U.S. Carvedilol Trials program was four concurrent trials that evaluated carvedilol in heart failure.[6,10] Study subjects had symptomatic heart failure (NYHA class II–IV) and left ventricular ejection fraction at or below 0.35 despite therapy with ACE inhibitors, diuretics, and digitalis. A total of 696 patients were randomized to receive carvedilol and 398 to receive placebo. The trial was stopped early after an average of 7.5 months of follow-up because of a 65% reduction in mortality. The average number of admissions per patient for any cause was 0.40 ± 0.78 in the placebo group versus 0.30 ± 0.78 in the carvedilol group (relative risk reduction = 25%; $P = .003$). The average number of cardiovascular admissions per patient was 0.30 ± 0.69 in the placebo group versus 0.21 ± 0.57 in the carvedilol group (relative risk reduction = 30%; $P = .021$). The average number of heart failure admissions per patient was 0.15 ± 0.54 in the placebo group versus 0.07 ± 0.34 in the carvedilol group (relative risk reduction = 53%; $P = .028$). Table 1 shows the percentage of subjects hospitalized in the placebo and carvedilol groups. Overall there was a 29% reduction in the percentage of patients hospitalized with the addition of carvedilol.

The effect of carvedilol and placebo therapy on inpatient resource utilization and costs for cardiovascular hospitalization is summarized in Table 2. When analyzed per patient, carvedilol therapy was associated with significant reductions in total days in the hospital (−49%), days in an intensive care unit (−77%), and hospital costs of care (−37%). When analyzed per stay, there was a significant reduction in the utilization of intensive care with carvedilol (−90%) and trends for fewer days per stay and fewer hospital costs per stay.

The MERIT-HF Trial

The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial evaluated the effect of metoprolol succinate on survival in heart failure. Subjects had symptomatic heart failure (NYHA functional class II–IV) and left ventricular ejection fraction at or below 0.40 despite treatment with ACE inhibitors, diuretics, and digitalis. A total of 1990 subjects were randomized to metoprolol and 2001 subjects to placebo. Of these subjects, 581 metoprolol subjects (29%) and 668 placebo subjects (33%) experienced at least one hospitalization ($P = .004$). The total number of hospitalizations in the metoprolol group was 1012 versus 1149 in the placebo group ($P = .005$). The total number of days in the hospital in the metoprolol group was 10,172 versus 12,262 in the placebo

Table 2
Effect of Carvedilol on Cardiovascular Hospitalizations

Measure	Placebo (n = 398)	Carvedilol (n = 696)	% Difference	*P*
Per patient				
Days in hospital	3.08 ± 11.72	1.56 ± 5.70	−49%	.019
Days in ICU/CCU	1.46 ± 9.69	0.33 ± 1.65	−77%	.011
Hospital costs	$4463 ± $20,565	$1912 ± $7595	−57%	.016
Per stay				
Days in hospital	10.81 ± 18.01	7.39 ± 6.55	−32%	.298
Days in ICU/CCU	5.61 ± 18.07	1.49 ± 2.58	−73%	.049
Hospital costs	$16,426 ± $35,377	$9318 ± $11,304	−43%	.097

Data in placebo and carvedilol columns are mean plus or minus standard deviation.
ICU/CCU, intensive care unit/critical care unit.
Data from Fowler et al,[10] with permission.

group ($P = .004$). As shown in Figure 2, metoprolol therapy was associated with an 18% reduction in the number of patients hospitalized for all causes, a 25% reduction in the number of patients hospitalized for cardiovascular causes, and a 35% reduction in patients hospitalized for worsening heart failure.

The CIBIS-II Trial

The Cardiac Insufficiency Bisoprolol Study (CIBIS-II) trial evaluated the effect of bisoprolol upon survival in heart failure.[8] Subjects had symptomatic heart failure (NYHA functional class III and IV) and left ventricular ejection fraction at or below 0.35 despite treatment with ACE inhibitors, diuretics, and digitalis. A total of 1320 subjects were randomized to bisoprolol and 1327 subjects to placebo. Of these subjects, 440 bisoprolol subjects (33%) and 513 placebo subjects (39%) experienced at least one hospitalization (risk reduction = 20%; $P = .0006$). Bisoprolol was associated with a 36% reduction in patients with heart failure hospitalization ($P = .001$). The treatment costs per patient for bisoprolol and placebo were estimated in France, Germany, and the United Kingdom.[11] As can be seen in Table 3, bisoprolol treatment was associated with lower treatment costs in all three countries.

COPERNICUS

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial evaluated the effect of carvedilol upon survival in heart failure.[9] Subjects had shown symptoms at rest or during any activity for at least 2 months and left ventricular ejection fraction at or below 0.25 despite treatment with ACE inhibitors and diuretics (therapy with digitalis and/or amiodarone was permitted). Compared to other multicentered trials of β-blocker therapy for heart failure, subjects in the COPERNICUS trial had the most advanced disease, as evidenced by the highest placebo mortality rate (19.7%). A total of 1133 subjects were randomized to carvedilol and 1156 subjects to placebo. Carvedilol therapy was associated with a 27% reduction in total days in the hospital ($P = .0005$), a 20% reduction in the number of hospital admissions ($P = .0017$), and a 9% reduction in days per admission ($P = .015$).

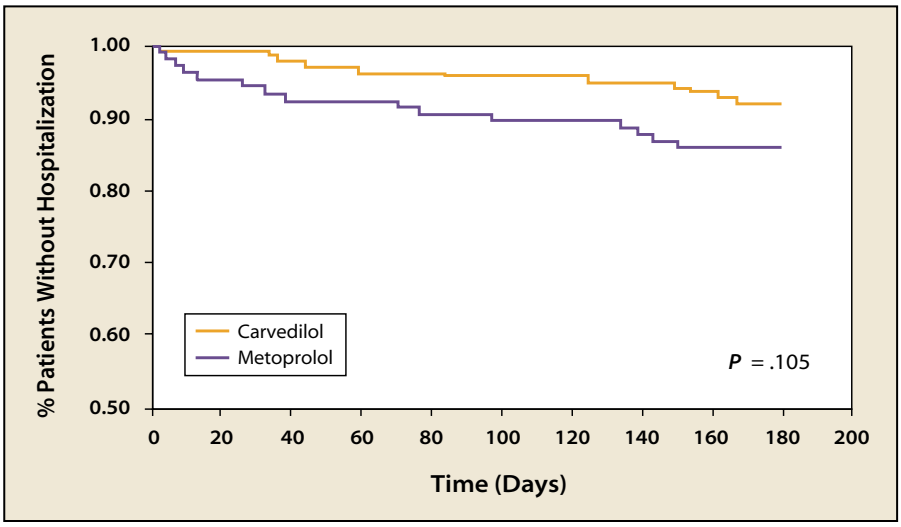

Figure 2. *Percentage of patients without hospitalization on either carvedilol or metoprolol in a claims analysis of six health care plans. Six-month hospitalization was significantly lower for patients receiving carvedilol compared to metoprolol. Adapted from Luzier et al,[14] with permission.*

Patients who survive will accrue greater health care costs than patients who die prematurely.

The Cost-Effectiveness of Beta-Blocker Therapy for Heart Failure

Because β-blocker therapy improves survival, a simple calculation of health care costs of β-blocker therapy for heart failure would be misleading. It is obvious that patients who survive will accrue greater health care costs than patients who die prematurely. Therefore it is much more useful to assess the effect of therapy upon cost-effectiveness. The cost-effec-

Table 3
Estimated Cost per Patient Treated in CIBIS-II

	Placebo	Bisoprolol
France	FF 35,009	FF 31,762
Germany	DM 11,563	DM 10,784
United Kingdom	£4987	£4722

CIBIS-II, the Cardiac Insufficiency Bisoprolol Study.

tiveness of a new therapy can be defined as the ratio of the difference (new therapy minus conventional therapy) in expected lifetime medical care costs to the corresponding difference in life expectancy. This type of analysis not only estimates the cost per life-year saved but also makes it easier to compare a new therapy to therapies that have become the standard of care.

Delea and coworkers[12] examined the cost-effectiveness of carvedilol therapy in the U.S. Carvedilol Trials program. They used a Markov model to project life expectancy and lifetime medical care costs for a hypothetical cohort of patients with heart failure assumed to receive carvedilol plus conventional therapy or conventional therapy alone. The benefits of carvedilol were projected under two alternative scenarios. In one scenario ("limited benefits"), the benefits were assumed to persist only for 6 months (average follow-up in the trial) and then end abruptly. In the other ("extended benefits"), they were assumed to persist for 6 months and then decline gradually over time, vanishing by the end of 3 years. For patients receiving conventional therapy alone, estimated life expectancy was 6.67 years. For patients receiving carvedilol and conventional therapy, estimated life expectancy was 6.98 years for the limited benefits scenario and 7.62 years under the extended benefits scenario. The authors estimated that the expected lifetime costs of heart failure–related care to be $28,756 for conventional therapy and $36,420 and $38,867 for carvedilol (limited and extended benefits scenario, respectively). Thus the cost per life-year saved for carvedilol was estimated to be $29,477 and $12,799 under the limited and extended benefits assumptions, respectively.

Gregory and coworkers used different methods to estimate cost per life-year saved for bisoprolol, metoprolol, and carvedilol.[13] Their model used estimates based on Medicare claims data from a 5% sample of patients in Massachusetts in 1995. Outcomes were extrapolated from the published results of prospective clinical trials. They estimated the incremental costs to be $15,656 for carvedilol, $2613 for metoprolol (assuming drug therapy cost with the use of generic metoprolol tartrate, not metoprolol succinate), and $3455 for bisoprolol. The increase in life expectancy was estimated to be 2.4 years for carvedilol, 1.1 years for metoprolol, and 1.0 years for bisoprolol. Thus the cost per life-year saved was estimated to be $6740 for carvedilol, $2472 for metoprolol, and $3336 for bisoprolol. It is clear that the author's results are sensitive to their estimates of the cost of drug therapy as well as the relative mortality rate for the different β-blockers. Note that their estimates for the cost per life-year saved for carvedilol were significantly lower than the estimates by Delea. However, even the highest estimates of cost per life-year are well below accepted standards of cost-effectiveness.

Luzier and coworkers compared resource use and cost in heart failure patients receiving metoprolol with carvedilol by use of a retrospective reimbursement-claims analysis.[14] Resource use and cost data were extracted for heart failure patients who were treated with either metoprolol or carvedilol for 6 months after the initiation of β-blocker therapy by use of claims submitted to six health care plans. As this was

Main Points

- Approximately 1% of adults in their fifties have a diagnosis of heart failure and 10% of 80-year-olds suffer from this syndrome; heart failure is now the most common primary admission diagnosis in patients older than 65 years.
- The annual costs for caring for patients with heart failure is estimated to range from $10 billion to nearly $40 billion; heart failure now accounts for over 5% of total health care expenditures, and inpatient care contributes between 60% and 75% of this total expense.
- Several trials have shown reduction in hospitalization with the addition of β-blocker therapy to angiotensin-converting enzyme inhibitors and diuretics with or without digitalis.
- The U.S. Carvedilol Trials program was stopped early after an average of 7.5 months of follow-up because of a 65% reduction in mortality. Overall there was a 29% reduction in the percentage of patients hospitalized with the addition of carvedilol.
- The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure found a 25% reduction in the number of patients hospitalized for cardiovascular causes and a 35% reduction in patients hospitalized for worsening heart failure.
- The Cardiac Insufficiency Bisoprolol Study (CIBIS) found that bisoprolol treatment was associated with lower treatment costs in France, Germany, and the United Kingdom.
- The cost-effectiveness of β-blocker therapy compares favorably to that of other generally accepted medical interventions.

a retrospective analysis, β-blocker use was assigned by physician preference, not by randomization. Claims from 139 carvedilol and 106 metoprolol patients were analyzed. Comorbidity was similar for the two β-blocker groups, based on a modified Charlson index. Compared to metoprolol patients, carvedilol patients experienced fewer total hospitalizations (62% vs 36%; $P < .001$) and emergency room visits (43% vs 24%; $P = .002$). As can be seen in Table 1, carvedilol treatment was associated with a significant decrease in the risk of any hospitalization (adjusted odds ratio = 0.35, 95% confidence interval .20–.63; $P < .001$). Although carvedilol was associated with higher pharmacy costs (mean $1677 for carvedilol versus $1322 for metoprolol; $P < 0.001$), total costs were significantly lower (mean $8100 for carvedilol versus $14,475 for metoprolol; $P = .025$). The fact that treatment was not randomized is an obvious limitation of this study. Despite such shortcomings, this study is unique because the authors analyzed actual insurance claims, not estimates based on historical claims data.

Summary

Beta-blocker therapy reduces the number and duration of hospitalization of patients with heart failure. This benefit has been observed in multiple clinical trials using carvedilol, metoprolol, or bisoprolol. Patients with mild, moderate, or severe heart failure all appear to benefit from the addition of β blockade to conventional therapy. The cost-effectiveness of β-blocker therapy compares favorably to that of other generally accepted medical interventions. Comparisons between β-blockers are difficult due to the multiple assumptions used in the various published models. The ongoing Carvedilol Or Metoprolol European Trial (COMET), which is a prospective, randomized trial of carvedilol versus metoprolol, should give additional data on the relative cost effectiveness of these two drugs. ■

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