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Incremental Cost-Effectiveness of Guideline-Directed Medical Therapies for Heart Failure

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Objectives This study sought to quantify the incremental cost-effectiveness ratios (ICER) of angiotensin-converting enzyme inhibitor (ACEI), beta-blocker (BB), and aldosterone antagonist (AldA) therapies for patients with heart failure with reduced ejection fraction (HFrEF).

Background There are evidence-based, guideline-directed medical therapies for patients with HFrEF, but the incremental cost-effectiveness of these therapies has not been well studied using contemporary data.

Methods A Markov model with lifetime horizon and two states, dead or alive, was created. We compared HFrEF patients treated with diuretic agents alone to three treatment arms: 1) ACEI therapy alone; 2) ACEI+BB; and 3) ACEI+BB+AldA. Sequential therapy was also analyzed. HF hospitalizations and mortality rates were based on representative studies. Costs of medications and inpatient and outpatient care were accounted for.

Results Treatment with ACEI and ACEI+BB strictly dominated treatment with diuretics only (cost-saving). The greatest gains in quality-adjusted life-years occurred when all 3 guideline-directed medications were provided. The incremental cost-effectiveness ratio (ICER) of ACEI+BB+AldA versus ACEI+BB and ACEI+BB versus ACEI was <$1,500 per quality-adjusted life-year. The cost-savings in the ACEI and ACEI+BB cohorts compared to that with diuretics alone were $444 and $33, respectively. Assuming lower treatment costs and lower hospitalization rates in the ACEI+BB+AldA arm resulted in greater cost-savings. Even in the most unfavorable situations, the ICER was <$10,000 per life-year gained.

Conclusions Our analysis demonstrates that medical treatment of HFrEF is highly cost-effective and may even result in cost-savings. Greater efforts to ensure optimal adherence to guideline-directed medical therapy for HFrEF are warranted. (J Am Coll Cardiol 2013;61:1440–6) © 2013 by the American College of Cardiology Foundation

Heart failure (HF) remains one of the leading causes of mortality, morbidity, and health care-associated costs worldwide. Approximately 6 million Americans have HF, and the lifetime risk of developing HF is 1 in 5 (1,2). After a HF hospitalization, 5-year mortality for HF is over 40% (3,4). There are also substantial costs associated with HF, including over 1 million HF admissions a year and $39.2 billion a year from direct and indirect costs (5).

Over the past 2 decades, there have been remarkable advances in medical therapy for HF with reduced ejection fraction (HFrEF). The use of angiotensin-converting enzyme inhibitors (ACEI), beta-blockers (BB), and aldosterone antagonists (AldA) has resulted in substantial reductions in mortality, morbidity, and hospitalizations in HFrEF patients (6–8). Previous studies conducted when these medications were available only as branded therapies have shown that the cost-effectiveness of these therapies in patients with mild to moderate HFrEF were $100 to $25,000 per quality-adjusted life-year (QALY) compared to that with conventional treatment (9–13).

However, now that ACEI, BB, and AldA have generic formulations available, we hypothesized that guideline-directed medical therapies for HFrEF will be of even greater value and possibly cost-saving. In addition, the incremental cost-effectiveness for each therapy has not been previously evaluated using contemporary data, including costs associated with generic formulations and use of AldA plus BB plus ACEI (AldA+BB+ACEI) therapy in chronic HFrEF. Our objective was to quantify the incremental cost-effectiveness of ACEI, BB, and AldA therapies and the cost-effectiveness of these therapies compared to that with

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background diuretic therapy in patients with mild to moderate HFrEF.

Methods

Markov models are commonly used to understand cost-effectiveness of therapies in chronic diseases. We created a Markov model to simulate costs, QALYs, and incremental cost-effectiveness of patients with HFrEF receiving ACEI, BB, and AldA in a cohort of hypothetical patients with mild to moderate (New York Heart Association [NYHA] class II or III) HF. Our model had a lifetime horizon, was U.S. based, and consisted of two states: dead or alive. We attempted to take the perspective of a lifetime single-payer/vertically integrated healthcare system providing full coverage for hospitalizations, office visits, laboratory tests, medications, and resources to the extent possible with available cost data. The length of follow-up in the representative studies of medical treatment for HF ranged from 12 to 41 months. We conservatively assumed that benefits for the medical therapies lasted 2 years but that the costs of treatment continued indefinitely. From year 3 until death, the cohort reverted to having the same mortality and hospitalization rates as the cohort receiving only diuretic agents. We factored in the additional mortality seen with increasing age based on U.S. lifetime tables (14). All costs and QALYs were discounted at 3% and were in 2012 U.S. dollars.

The placebo arm of the SOLVD (Study of Left Ventricular Dysfunction), a large trial that has been used as the basis for disease estimates by other studies, served as the base (diuretic-only cohort) population in this study (6). Patients included in this trial were HF patients with ejection fractions of 35% or less and were treated with oral loop diuretics. The mean age of patients in this study was 61 years of age, and 90% were in NYHA functional class II or III. This group of patients represents the overall population of patients in our cohort, defining "baseline" risk in this study. We compared our baseline cohort (treatment with diuretic-only cohort) to those in three treatment arms: patients receiving: 1) ACEI; 2) ACEI+BB; or 3) ACEI+BB+AldA therapy. We also compared each incremental therapy to the previous therapy: 1) ACEI+BB versus ACEI; and 2) ACEI+BB+AldA versus ACEI+BB therapy.

Hospitalizations. Probabilities of hospitalization for the baseline and ACEI cohorts were derived from the SOLVD, as that study was the most representative of outcomes for patients in our diuretic-only and ACEI cohorts (6). Total number of hospitalizations for HF at the end of the trial was divided by the number of people in each arm and the average follow-up (41 months) to estimate the yearly probability of hospitalization per person. The difference in deaths or hospitalizations between the 2 groups did not converge at the end of the trial (41 months), but we conservatively assumed that this decrease in hospitalization was only in the first 2 years of our model.

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor

AldA = aldosterone antagonists

BB = beta-blocker

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICER = incremental cost-effectiveness ratio

QALY = quality-adjusted life-year

We derived the yearly probability of HF hospitalization for the ACEI+BB group by multiplying the yearly probability of HF hospitalization for the ACEI group by "$1 - x$, x = the relative risk reduction for HF hospitalization" in the MERIT-CHF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure) study (relative risk reduction: 31.6%), a study representative of the effects of BB+ACEI on HFrEF (7). We then derived the yearly probability of HF hospitalizations for the ACEI+BB+AldA cohort from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial, a study representative of the effects of ACEI+BB+AldA on HFrEF (8). That study showed a hazard ratio of 58% for HF hospitalizations for patients taking ACEI+BB+AldA compared to those taking ACEI+BB. The hazard ratio from this study was calculated with a median follow-up of 21 months (we assumed this was equivalent to 24 months), so we calculated the yearly hazard ratio by taking the square root of the 2-year hazard ratio (i.e., $\sqrt{x}$ = 1 year hazard ratio, x = 2 year hazard ratio). We then multiplied the yearly hazard ratio by the probability of HF hospitalizations in the ACEI+BB cohort. In both the EMPHASIS-HF and MERIT-HF trials, the event curves for deaths and HF hospitalizations continued to diverge at the end of follow-up (average of 21 and 12 months, respectively) (Table 1).

Costs. The costs taken into account in our model included HF-related hospitalization, medications and medication monitoring, and ambulatory care (Table 2). The average cost of one inpatient hospitalization, based on the report by Delea et al. (15), was multiplied by the probability of hospitalization each year (as derived above) to obtain the average yearly cost attributed to inpatient hospitalization per patient. The probability of hospitalization accounted for some patients requiring multiple hospitalizations in 1 year. We conservatively assumed that the benefits for the medical therapies lasted 2 years but that the costs of treatment continued until death. The cost of ambulatory care was based on the ambulatory care in the SOLVD trial (9). The costs of medications were based on the prices of 30-day prescriptions for generic medications (16). For base our models, we excluded the costs of non-HF hospitalizations. Based on our clinical experience, we assumed that the ACEI and ACEI+BB cohorts required four basic metabolic panel tests and that the ACEI+BB+AldA cohort required six basic metabolic panel tests in the first year. We assumed that our base cohort and all cohorts after year 2 required three metabolic panels a year because of diuretic use. The