Agency for Healthcare Research and Quality

Evidence Report/Technology Assessment

Number 82

Pharmacologic Management of Heart Failure and Left Ventricular Systolic Dysfunction: Effect in Female, Black, and Diabetic Patients, and Cost-Effectiveness

Summary

Overview

Heart failure (HF) is associated with substantial morbidity and mortality; it is a primary or secondary cause of death for approximately 250,000 people per year in the United States. According to the *2002 Heart and Stroke Statistical Update* (www.americanheart.org), HF was the first-listed diagnosis for 962,000 hospitalizations in 1999, and it is the most common diagnosis among hospital patients age 65 and older. In fact, 20 percent of all hospitalizations in this age group carry a primary or secondary diagnosis of HF. Over 3 million outpatient office visits each year are related to this illness. In 1998 alone, the estimated annual direct cost due to HF was $18.8 billion.

A series of studies has established that angiotensin-converting enzyme inhibitors (ACE inhibitors) and beta-adrenergic blocking agents (beta-blockers) provide life-saving benefits in patients with HF and left ventricular systolic dysfunction. However, most of the patients enrolled in such studies have been white males. Thus, a clinical question that is repeatedly asked is whether the mortality benefit reported in these clinical trials is also achieved for particular subpopulations, such as women, people of other races, and patients with various comorbidities such as diabetes mellitus or renal insufficiency. Since few of the randomized trials enrolled enough women, blacks, or patients with comorbidities to have sufficient statistical power to support conclusions based on subgroup analysis, this question is appropriate for meta-analysis.

In addition, because the clinical trial data support a mortality benefit for patients with asymptomatic left ventricular dysfunction, it is natural to question both the cost-effectiveness of such treatment and that of screening asymptomatic patients for left ventricular dysfunction. These clinical and policy questions form the basis for this report.

Reporting the Evidence

AHRQ defined the scope of work for this project to include an evidence report and quantitative analysis on the effectiveness of treatment for HF using ACE inhibitors and beta-blockers. This topic was nominated by the American College of Physicians, the American Society of Internal Medicine, and the American Academy of Family Physicians. This group submitted the following potential key questions to AHRQ:

1. What evidence exists on the effectiveness of nurse management programs and health food supplements?
2. What evidence exists on the treatment of sleep apnea in patients with HF?
3. What is the evidence on the treatment of specific myocardial disorders, e.g., myocarditis, sarcoidosis, and amyloidosis, in patients with HF?
4. What interventions are effective for patients with diastolic dysfunction?
5. Which patients benefit from which beta-blockers?
6. What are the effects of potassium levels on HF outcomes?

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service

7. Do angiotensin blockers improve outcomes?
8. What, if any, are the differences in treatment effectiveness associated with patient gender, race, age, and income level?

After congestive heart failure was nominated as a topic, but prior to assignment of this contract to the Southern California Evidence-based Practice Center (SCEPC), the American Heart Association (AHA) and the American College of Cardiology (ACC) released practice guidelines on the management of HF. AHA/ACC graciously provided the SCEPC with a draft copy for our confidential review. On September 8, 2000, a conference call was held with our technical expert panel (TEP) to limit the key questions to be addressed in the evidence report. The purpose of the conference call was to identify topic areas for this report that would complement but not duplicate the draft guidelines, a copy of which had been made available to each TEP member. The technical experts judged that several of the original key questions posed by the nominating organizations had been answered adequately in the AHA/ACC guidelines, major studies were under way that would answer several more of the questions, and published data would be insufficient to reach meaningful conclusions for other questions. The TEP identified three areas in which they believed significant contributions could still be made:

- Assessment of the effects of age over 70, gender, race, and assisted living on treatment outcomes.
- Cost-effectiveness of medication combinations.
- Assessment of outcomes in patients with various comorbidities, particularly diabetes mellitus, renal dysfunction, and cognitive dysfunction.

This evidence-based report addressed the following key questions regarding pharmacologic management of heart failure and left ventricular systolic dysfunction:

1. Are angiotensin-converting enzyme inhibitors (ACE inhibitors) and beta-adrenergic blocking agents (beta-blockers) effective in patients with HF and left ventricular systolic dysfunction and does this effectiveness differ in the following subpopulations: men, women, blacks, whites, diabetics, and nondiabetics?
   a. What is the association between treatment with ACE inhibitors and beta-blockers and all-cause mortality for female, male, diabetic, nondiabetic, black, and white patients with HF?
   b. Does this association vary (e.g., are there statistically significant differences) by gender (female versus male), diabetic condition (those with diabetes versus those without), and race (black versus white patients)?
2. What is the cost-effectiveness of both treatment of and screening for asymptomatic left ventricular systolic dysfunction?

Methodology

Literature Review and Meta-Analyses

To answer key questions 1a and 1b, we first retrieved all articles that pertained to eleven large randomized placebo-controlled studies on ACE inhibitors and beta-blockers. Because the SOLVD study actually consisted of two distinct trials (one on prevention and one on treatment), we included twelve studies in total. Meta-analyses were performed separately for the ACE inhibitor and beta-blocker studies. The common outcome of interest was all-cause mortality. For some studies, both patient-level data and published summary data were available; if the two disagreed, we always chose the patient-level statistics over published group-level statistics. Among the five studies for which we had patient-level data, three datasets had minor disagreements with related publications.

All reports that presented the relevant patient sub-population data did so in the form of a two-by-two table of all-cause mortality by treatment (or placebo) group for each sub-population. Alternatively, if we were given the patient-level data, we could construct this table directly. For example, an ACE inhibitor study might provide separate two-by-two tables for men and women.

To answer key question 1a, for each sub-population (e.g., women), we estimated the log mortality relative risk, which is equal to the log of the risk of dying for women who received ACE inhibitors divided by the risk of dying for women who received placebo. The standard error for the log relative risk was also estimated, and a 95 percent confidence interval was constructed. A similar log relative risk and confidence interval were calculated for men. We then back-transformed to the unlogged scale for interpretability so that our final statistic for each sub-population in each study was the relative risk with its associated confidence interval. The analysis informed us about the association between various patient characteristics, such as gender and mortality, with that association measured on the relative risk scale.

To answer key question 1b, that is, whether the association differed between sub-populations (e.g., female versus male), we determined whether statistical differences existed between the relative risks for two subpopulations. We did this by constructing a test statistic equal to the ratio of relative risks (RRR), which equals the female relative risk divided by the male relative risk, for example. If this test statistic differs significantly from 1, then we infer that the relative risks for the two subgroups are significantly different. As before, we performed the analysis on the log scale. The log ratio of relative risks equals the log of the relative risk for women divided by the relative risk for men, and its standard error equals the square root of the sum of the variances of the two log relative risks. We constructed a confidence interval on the log scale. We

then back-transformed the estimate and its confidence interval to the unlogged scale so that our final test statistic for each study was the ratio of relative risks.

Because the followup times varied across studies and calculating the relative risk does not take this variation (or the censoring of observations) into account, we also assessed the mortality associated with ACE inhibitors and beta-blockers respectively on the hazard ratio scale. The majority of our studies presented hazard ratios and confidence intervals, and after transforming these statistics to the log scale, we extracted the log hazard ratio and its standard error for each study. We estimated the log hazard ratio for each patient subgroup of interest for each study that provided the data stratified on that dimension. We followed the same analytic strategy for the hazard ratio as for the relative risk, conducting a random-effects pooled analysis on the log scale, and back-transforming to the unlogged scale. We then constructed a ratio of hazard ratios (RHR) to compare the hazard ratios in each subgroup.

For each drug and patient comparison subgroup of studies, we assessed the possibility of publication bias by evaluating a funnel plot of the individual study log relative risks and hazard ratios. In addition, we performed a sensitivity analysis, because studies varied in their definitions of racial groups. For racial comparisons, if the study provided data separately by racial subgroup, we utilized those data. If the data were not stratified in that way, we used data for black versus nonblack patients. Our last choice was data for nonwhite versus white patients. For those studies that described the data in more than one of these ways, we compared the relative risk and hazard ratio statistics.

Cost-Effectiveness Analyses

To address key question 2, we developed a decision model to assess the cost-effectiveness of treatment for asymptomatic left ventricular dysfunction, using EXCEL (Version 5.0, Microsoft Corporation, Redmond, WA) and DATA (Version 3.0, TreeAge Software, Boston, MA) software. Using two treatment strategies, we modeled the lifetime health and economic outcomes for a hypothetical cohort of 55-year-old asymptomatic patients with ejection fraction of 35 percent or less but no history of HF. In the first strategy, asymptomatic patients are treated with ACE inhibitors. In the second strategy, patients are not treated with ACE inhibitors until they develop symptomatic HF.

During each time period of interest (e.g., 1 month), patients with no history of HF can remain asymptomatic, develop heart failure, or die. Of those patients who developed HF, we assumed 33 percent would be hospitalized during their initial episode. Once patients develop HF, they can remain in stable heart failure, be hospitalized, or die during each time period. The model follows each patient until death.

We also developed a decision model to assess various screening options for reduced left ventricular ejection fraction. We examined six screening strategies:

1. Echocardiography for all patients. Patients with an ejection fraction less than 35 percent are treated (ACE inhibitors) to prevent development of HF.
2. Electrocardiography (ECG) first, and if abnormal, echocardiography.
3. Blood test for B-type natriuretic peptide (BNP) first and, if abnormal, echocardiography.
4. ECG only, with treatment based on the results.
5. BNP only, with treatment based on the results.
6. No screening for depressed left ventricular function.

Each screening option has one of four possible outcomes: true positive, false positive, true negative, or false negative. In our model, only true and false positives are treated. True-positive patients have a higher quality-adjusted survival than false negatives, who are treated only when HF develops. True-negative patients have a normal age-specific life expectancy. False-positive patients receive a small decrement in quality-adjusted survival to account for potential side effects of treatment.

We generated the lifetime health and economic outcomes for hypothetical cohorts of 55-year-old patients with (1) depressed ejection fraction (35 percent or less) but no history of HF treated with ACE inhibitors, (2) depressed ejection fraction but no history of HF and no treatment until HF developed, and (3) patients without depressed ejection fraction. Each month, patients with a depressed ejection fraction and without a history of HF can remain asymptomatic, develop HF, or die. Of those patients who develop HF, we assumed that 33 percent would be hospitalized during their initial episode. Once patients develop HF, they can remain in stable HF, be hospitalized, or die during each time period. The model follows each patient until death.

Findings

ACE Inhibitors

Effects of gender. For seven studies, we were able to obtain gender-stratified data to calculate the effect of ACE inhibitors on mortality. The data from one study could be used only in the RRR assessment, and the data from another could be used only in the RHR assessment. In aggregate, these studies included 2,898 women and 11,674 men and ranged in duration from 6 months to 42 months. The pooled random-effects estimates from the six studies with relative risk data yielded values of 0.82 for men (95% CI: 0.74, 0.90) and 0.92 for women (95% CI: 0.81, 1.04). The corresponding pooled random-effects estimates from the six studies with hazard ratio data yielded values for the men of 0.76 (95% CI: 0.66, 0.87)

and for women of 0.84 (95% CI: 0.72, 0.98.) The difference in effect between men and women approached statistical significance for the ratio of relative risks (p = 0.07).

This difference between the estimates of relative risk and hazard ratios is due to the inclusion in the hazard ratio analysis of the AIRE study, which reported a slight nonsignificant mortality benefit for women compared to men treated with ramipril. In contrast, the relative risk analysis included the SAVE study, which reported a distinct but non-statistically significant higher mortality in women relative to men treated with captopril (RRR = 1.24). In a subgroup analysis, studies were divided into those that treated symptomatic HF (risk ratio analysis for CONSENSUS, SOLVD-treatment, and TRACE; hazard ratio analysis for AIRE, CONSENSUS, SOLVD-treatment, and TRACE) and those that treated for asymptomatic left ventricular systolic dysfunction (risk ratio analysis for SAVE, SOLVD-prevention, and SMILE; hazard ratio analysis for AIRE, SOLVD-prevention, and SMILE). The difference in efficacy between men and women is most pronounced for treatment of asymptomatic left ventricular dysfunction, where the evidence does not support or suggest a mortality benefit for women (relative risk = 0.96; 95% CI: 0.75, 1.22).

The evidence indicates that women with symptomatic heart failure benefit when treated with ACE inhibitors, although the benefit may be somewhat less than that seen in men. However, the evidence does not support a mortality benefit from ACE inhibitors in women with asymptomatic left ventricular systolic dysfunction.

Differences between diabetics and nondiabetics. We were able to obtain data stratified by co-occurrence of diabetes from six studies to calculate the effect of ACE inhibitors on mortality. In aggregate, these studies included 2,398 patients with diabetes and 10,188 patients without diabetes. All of these studies contributed data to our relative risk analysis; however, one study did not contain data that we could use for our hazard ratio analysis. Both analyses yielded similar results. The random-effects pooled estimate of the relative risk of mortality in patients with diabetes is 0.84 (95% CI: 0.70, 1.00) while the estimate of the relative risk in patients without diabetes is 0.85 (95% CI: 0.78, 0.92). The corresponding estimates for the hazard ratio are 0.73 (95% CI: 0.56, 0.95) for diabetics and 0.80 (95% CI: 0.69, 0.93) for nondiabetics. These results indicate that both patients with diabetes and patients without diabetes achieve reductions in mortality when treated with ACE inhibitors for HF.

Effects of race. We were able to obtain data stratified by patient race from three studies to assess the effects of ACE inhibitors on mortality. The remaining ACE inhibitor studies were conducted primarily in Scandinavian and European countries and did not enroll substantial numbers of black patients. Because one study did not present data that allowed us to calculate the hazard ratios, we had an insufficient number of studies to pool for this analysis. Therefore, only a pooled relative risk analysis was performed, which yielded an estimate in white patients of 0.89 (95% CI: 0.82, 0.97) and an estimate in black patients of 0.89 (95% CI: 0.74, 1.06). These data provide no evidence that black patients achieve lesser or greater reductions in mortality than white patients when treated with ACE inhibitors for HF. While the relative risk reduction in black patients did not achieve conventional level of statistical significance, the estimate of effect is the same as the statistically significant reduction seen in white patients. Furthermore, the two estimates of effect (for black and white patients) do not statistically differ from each other. These results are consistent with the analysis by the SOLVD investigators, who reported that there was no significant difference in mortality reduction among black and white patients in the SOLVD studies. (However, these investigators did report a difference in hospitalization rate in black patients compared to white patients.)

Beta-Blockers

Effects of gender. Five studies provided gender-stratified data on the effect of beta-blocker treatment on mortality. One study contributed data only to the relative risk analysis. Our TEP determined that bucindolol, the beta-blocker evaluated in BEST, was sufficiently different in action from the other beta-blockers to justify excluding the BEST study from pooled analysis. In aggregate, the pooled studies included 2,134 women and 7,885 men. Both analyses yield similar results. The random-effects pooled estimate for the relative risk on mortality for women was 0.63 (95% CI: 0.44, 0.91), while for men the estimate was 0.66 (95% CI: 0.59, 0.75). The corresponding values for the hazard ratio analysis were 0.62 (95% CI: 0.34, 1.14) for women and 0.62 (95% CI: 0.52, 0.73) for men. Likewise, BEST reported equal effects in men and women (although in BEST, the reduction in all-cause mortality was not statistically significant). Our interpretation of these data is that both women and men with symptomatic HF have reduced mortality when treated with beta-blockers.

Differences between diabetics and nondiabetics. Three studies provided data stratified by co-occurrence of diabetes to calculate the effect of beta-blocker treatment on mortality. In aggregate, these studies included 1,883 patients with and 7,042 patients without diabetes. The only pooled estimates that were possible were the relative risks and they yielded a value of 0.65 (95% CI: 0.57, 0.74) for nondiabetic patients and a value of 0.77 (95% CI: 0.61, 0.96) for diabetic patients. This difference in relative risk was not statistically significant; however, the 95 percent confidence interval was very broad. Our interpretation

of these data is that in patients with HF, with or without diabetes, beta-blocker treatment is associated with reduced mortality.

Effects of race. Four studies provided race-stratified data to assess the effects of beta-blocker treatment on mortality. As mentioned above, BEST was judged to be clinically dissimilar to the other studies and was not included in the pooled analysis. In addition, one study was conducted in Scandinavian and European countries and did not enroll appreciable numbers of black patients. In aggregate, the three studies included in the pooled analysis included 545 black patients and more than 6,000 white patients. Both the relative risk analysis and the hazard ratio analysis yielded similar results. The pooled random-effects estimate of the relative risk of the effect on mortality for blacks was 0.67 (95% CI: 0.39, 1.16), whereas for whites it was 0.63 (95% CI: 0.52, 0.77). The corresponding pooled estimates from the hazard ratio analysis were 0.64 (95% CI: 0.36, 1.16) for black patients and 0.59 (95% CI: 0.45, 0.76) for white patients.

In contrast, the BEST trial showed a statistically significant racial difference in mortality for bucindolol treatment. In fact, the relative risk and hazard ratio for mortality exceeded 1 for blacks (although this was not statistically significant). Our interpretation of these data is that black patients are likely to have the same relative risk reduction as white patients treated with the beta-blockers bisoprolol, metoprolol, or carvedilol. Bucindolol, on the other hand, was associated with worse mortality outcomes in black patients than in white patients and may actually increase mortality in blacks.

Cost-Effectiveness Analysis

Assessing treatment of asymptomatic left ventricular dysfunction. For the base-case analysis of a 55-year-old man with an ejection fraction less than 40 percent and no history of symptomatic HF, the model predicted an average life expectancy without ACE inhibitor treatment of 8.1 years and a 5-year morbidity/mortality rate of 57 percent. These results are similar to the findings of the SOLVD prevention study. Treatment with ACE inhibitors improved survival and quality-adjusted survival by 8 months compared to no treatment. The lifetime cost of care was $3,718 greater for patients treated with ACE inhibitors than for those who received no treatment, with a cost per life-year gained of $5,802 and cost per quality-adjusted life year (QALY) gained of $5,644.

We tested the robustness of our base-case findings by varying the following assumptions: patient age, the risk of death with HF, the reduction in HF incidence, the reduction in risk of death for asymptomatic patients, the probability of hospitalization if symptomatic, cost of treatment, and quality of life. Treating asymptomatic patients with ACE inhibitors provided benefit compared to waiting for symptom development and remained economically attractive (< $20,000 per QALY gained) throughout the range of every variable tested.

Assessing screening for reduced left ventricular ejection fraction. For a population of asymptomatic 55-year-old individuals (prevalence of depressed ejection fraction 2.7 percent) we found that screening with echocardiography provided the greatest benefit but at a substantial cost. A strategy of initial screening with BNP followed by echocardiography improved outcome at a cost of only $18,300 per QALY gained compared to no screening. If quality of life is ignored, BNP screening costs $19,000 per life-year gained compared to no screening. The number needed to screen is 77 to gain 1 year of life and 70 to gain one QALY.

Because the cost-effectiveness ratio of screening with the ECG compared to no screening was greater than the ratio for BNP compared to ECG screening, the former strategy was eliminated as a possible screening option for the base-case cohort. Similarly, strategies of relying only on the ECG or BNP to determine treatment were eliminated, because they were more costly and provided fewer QALYs than the strategy using BNP followed by echocardiography.

We tested the robustness of our base-case findings by varying each of the following assumptions: prevalence of depressed left ventricular function, test characteristics of BNP, cost of testing, and impact of ACE inhibitors for patients with depressed ejection fraction. The decision to screen is influenced primarily by the prevalence of depressed ejection fraction and the accuracy of the screening tests and only slightly by the costs of screening, including echocardiography and BNP testing.

Conclusions

The following clinical conclusions can be reached from this evidence report. The evidence supported beneficial reductions in all-cause mortality with the use of beta-blockers in men and women, the use of ACE inhibitors in white and black patients, and the use of either drug in patients with diabetes.

We did, however, find evidence that suggests that women with asymptomatic left ventricular dysfunction may not have reduced mortality when treated with ACE inhibitors. The evidence we found does not constitute proof, and additional evidence of the effect of ACE inhibitors in women with asymptomatic left ventricular dysfunction is needed.

We also found conflicting evidence regarding the effect of beta-blocker use in black patients. Results of three of the beta-blocker studies suggested that white patients and black patients have similar reductions in all-cause mortality when treated with beta-blockers. However, the one study that assessed the beta-blocker bucindolol reported a statistically significant adverse effect on mortality in blacks relative to whites. These results suggest that not all beta-blockers have equivalent effects.

In our cost-effectiveness analyses, we found that treatment of asymptomatic left ventricular dysfunction with ACE inhibitors was cost-effective under virtually all assumptions, with typical costs of between $5,000 and $10,000 per QALY gained. Thus, this treatment is much more cost-effective than many other treatments considered standard medical practice. The demonstration of cost-effectiveness for treatment prompted an additional analysis to assess the cost-effectiveness of screening. This analysis showed that screening with BNP followed by echocardiography in a cohort of asymptomatic 55-year-old individuals was also cost-effective compared with other management strategies currently considered standard medical care. This strategy cost $19,000 per life year gained compared to a strategy without screening, with the number needed to screen equal to 77 to gain 1 year of additional life. These results were only modestly sensitive to cost and were most sensitive to the prevalence of asymptomatic depressed left ventricular ejection fraction. When the prevalence falls below about 1 percent, a strategy of screening becomes less cost-effective than commonly accepted thresholds for cost-effective care.

Future Research

The findings of this evidence report suggest several important areas for future research.

- Additional data are needed to support or refute the evidence that various beta-blockers may influence all-cause mortality differently in black patients. New placebo-controlled randomized clinical trials of beta-blocker therapy in black patients are likely the only way to answer this question definitively. Future studies of new or different beta-blocker drugs for heart failure need to include sufficient numbers of black patients to separately assess outcomes in this population, because a similar effect in black patients and white patients cannot be assumed.
- Further assessment of the effect of ACE inhibitors is needed in women with HF, particularly the effect on women with asymptomatic left ventricular dysfunction. It may be possible to answer this question by a more complete assessment of data from existing randomized clinical trials.
- Other outcomes of interest, including cardiac mortality, symptoms, and health care utilization, should be examined for all patient sub-populations. Individual patient-level data from the major randomized controlled trials may be sufficient to answer these and other original key questions regarding additional patient subpopulations (such as the aged and those with renal failure).

An additional implication of our findings is that researchers have not paid attention to ensuring that sufficient numbers of patients in important clinical subpopulations are enrolled in randomized trials. Such attention could obviate the need for future meta-analyses such as the ones on which this report is based.

If further research supports our findings of differential efficacy, additional research aimed at elucidating the cause for these findings should be undertaken. One possibility is that these findings do not represent differences in men and women or black patients and white patients, but rather reflect differing efficacy of these drugs according to the cause of heart failure (e.g., ischemic or nonischemic), which then may differ by sex or race. Alternatively, there could be a molecular basis for these results that differs by sex and race.

Given the robust evidence of benefit for ACE inhibitors and beta-blockers in reducing mortality, future work should also address how to improve the use of these therapies by focusing on potential barriers for practitioners and patients as well as empirically testing the conclusions of our cost-effectiveness analyses. Additional studies are needed to determine the true prevalence of asymptomatic left ventricular dysfunction, and to determine costs associated with making a new diagnosis of heart failure. Further research is needed to determine which patient characteristics identify a population at risk for left ventricular systolic dysfunction (prevalence greater than 1 percent). In addition, a study evaluating the health and economic outcomes of screening asymptomatic patient with BNP is warranted.

Availability of the Final Report

The full evidence report from which this summary was derived was prepared for AHRQ by the Southern California Evidence-based Practice Center based at RAND under contract number 290-97-0001. It is expected to be available in summer 2003. Printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 82, *Pharmacologic Management of Heart Failure and Left Ventricular Systolic Dysfunction: Effect in Female, Black, and Diabetic Patients, and Cost-Effectiveness.* When available, Internet users will be able to access the report online through AHRQ's Web site at: www.ahrq.gov.

www.ahrq.gov
AHRQ Pub. No. 03-E044
July 2003

ISSN 1530-440X