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Number 82

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

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

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Structured Abstract

Objectives. This evidence-based report had two objectives. The first objective was to assess whether angiotensin-converting enzyme inhibitors (ACE inhibitors) and beta-adrenergic blocking agents (beta-blockers) are effective in patients with left ventricular systolic heart failure and whether this effectiveness differs in the following subpopulations: men, women, blacks, whites, diabetics, and nondiabetics. The second objective was to assess the cost-effectiveness of both treatment of and screening for left ventricular systolic dysfunction.

Search Strategy. We conducted a thorough computerized library search and retrieved all articles that pertained to the twelve largest placebo-controlled studies on ACE inhibitors and beta-blockers. We also contacted leading experts in cardiology for unpublished data, contacted the authors of the clinical trials for patient-level data, and obtained patient-level data from the FDA.

Selection Criteria. We selected the twelve largest randomized placebo-controlled trials of ACE inhibitors and beta-blockers.

Data Collection and Analysis. We retrieved data through published articles or patient-level data files. For each, we estimated the mortality relative risk and hazard ratio for the subgroups of interest. For example, the relative risk of mortality for women is equal to the risk of dying for women who received the drug divided by the risk of dying for women who received a placebo. We pooled these statistics across studies. We then assessed whether these risks differed statistically via a ratio statistic. For example, to assess the relative effect of the drug on the relative risk of mortality for women as compared to men, we divided the relative risk in women by the relative risk in men to produce a ratio of relative risks. We pooled these statistics and tested whether the pooled ratio estimate was significantly different from 1.

In order to assess the cost-effectiveness of screening for and treating asymptomatic left ventricular dysfunction, we created a decision model. We modeled lifetime health and economic outcomes for a hypothetical cohort of 55-year-old asymptomatic patients with ejection fraction of 35% or less but no history of heart failure (HF), using two treatment strategies and six screening strategies.

Main Results. We found evidence, with two exceptions, that treatment with ACE inhibitors or beta-blockers reduces all-cause mortality in male, female, black, white, diabetic, and nondiabetic patients. The two exceptions were the use of ACE inhibitors in women and the use of beta-blockers in black patients. Regarding the former, we found clear evidence that treating women with symptomatic heart failure with ACE inhibitors was beneficial. However, the available evidence do not support a beneficial effect in women with asymptomatic left ventricular systolic dysfunction. Regarding black patients, treatment with the beta-blocker bucindolol was associated with a nonstatistically significant increase in all-cause mortality, while treatment with other beta-blockers was associated with a nonstatistically significant reduction in mortality of similar magnitude to the statistically significant reductions observed in white patients.

In our cost-effectiveness analyses, we found that treatment of asymptomatic left ventricular dysfunction with ACE inhibitors was very cost-effective under virtually all assumptions, with typical costs per quality-adjusted life-year gained of between $5,000 and $10,000. Additional

analysis showed that screening with B-type natriuretic peptide followed by echocardiography in a cohort of asymptomatic 55-year-old individuals was also cost-effective, compared with the costs of other therapies currently considered standard medical care. The number needed to screen in order to gain one year of additional life was 77. These results were only modestly sensitive to cost and were most sensitive to the prevalence of asymptomatic decreased left ventricular ejection fraction. When the prevalence falls below about 1%, a strategy of screening becomes less cost-effective than commonly accepted thresholds for cost-effective care.

Conclusions. ACE inhibitors and beta-blockers reduce mortality in a broad range of patients with left ventricular systolic dysfunction, including men and women, blacks and whites, and diabetics and nondiabetics. However, the value of ACE inhibitors in women with asymptomatic left ventricular systolic dysfunction is uncertain, and additional study is needed. In addition, based on data from a single study, the beta-blocker bucindolol may be associated with increased mortality in blacks, whereas other beta-blockers provide similar benefits in blacks and whites.

Treatment of asymptomatic left ventricular dysfunction with ACE inhibitors is very cost-effective. In addition, screening for asymptomatic left ventricular dysfunction with B-type natriuretic peptide followed by echocardiography is cost-effective in populations where the prevalence of this condition is 1% or greater.

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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?

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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.

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Evidence Report

Chapter 1. Overview

Heart failure (HF) is a clinical syndrome that can result from any cardiac disorder that impairs the ability of the ventricles to fill with and/or eject blood. The syndrome is characterized by signs and symptoms of intravascular and interstitial volume overload, which include shortness of breath and edema and/or manifestations of inadequate tissue perfusion, such as fatigue or poor exercise tolerance.

HF is a common medical condition that has a significant impact on public health. In the United States, an estimated 4.8 million individuals are affected by HF, and 400,000 to 700,000 new cases develop each year.[1] The prevalence of HF increases with age: It is present among 2% of persons age 40 to 59, more than 5% of persons age 60 to 69, and 10% of persons age seventy or older. In addition, a substantial number of individuals with asymptomatic ventricular dysfunction are at risk of developing symptomatic HF. Due to the aging of the American population, the incidence and prevalence of this disease are expected to increase markedly.

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% of all hospitalizations in this age group carry a primary or secondary diagnosis of HF. Over three million outpatient office visits each year are related to this disease. 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 or left ventricular systolic dysfunction. However, most of the patients enrolled in such studies have been white males. A clinical question that is consistently asked is whether or not the mortality benefit reported in these clinical trials is also achieved for other subpopulations, such as women, people of other races, and patients with particular comorbidities such as diabetes mellitus or renal insufficiency.

There are several reasons to expect that certain subpopulations might not achieve the same benefits as white males. Research evidence supports a lesser effect on blood pressure in black compared to nonblack hypertensive patients treated with ACE inhibitors,[2] and one of the ACE inhibitor trials reported a lesser effect of ACE inhibitors on reducing hospitalization for black compared to nonblack patients.[3] Similarly, men and women present and respond differently to particular cardiac therapies. Relevant to this topic, a preliminary analysis of one ACE inhibitor study suggested a trend toward lower mortality reduction in women than in men.[4] 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 additional, if 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 whether screening asymptomatic patients for left ventricular dysfunction is cost-effective. These clinical and policy questions form the basis for this report.

Chapter 2. Methodology

Scope of Work

AHRQ described the scope of work as a quantitative analysis and evidence report on the effectiveness of treatment of HF using ACE inhibitors and beta-blockers. The project had five key steps:

1. Identify technical experts to provide input and advice to the project.

2. Refine the research questions.

3. Perform a literature search and evaluation.

4. Systematically synthesize the evidence.

5. Produce and disseminate and evidence report.

Original Potential Key Questions

The American College of Physicians, the American Society of Internal Medicine, and the American Academy of Family Physicians nominated this topic. They submitted the following potential key questions to AHRQ.

1. What evidence exists on the effectiveness of nurse management programs? 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?

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?

Technical Expert Panel

Project staff assembled a technical expert panel (TEP) that included leading cardiologists working in academic and nonacademic settings, researchers, clinicians, and health care managers. Panelists assisted the project with topic refinement, retrieval of unpublished data, and review of the final evidence report. The TEP members (and relevant affiliations) are listed here:

Michael Barrett American College of Physicians
Greg Fonarow UCLA Medical Center
Barry Greenberg UCSD Medical Center
Paul Heidenreich Palo Alto VA Hospital
Stanford-UCSF Evidence-based Practice Center
Tom Knabel UnitedHealthcare
Marvin Konstam New England Medical Center
Michael Rich Washington University of School of Medicine
Anthony Steimle Kaiser Permanente, Northern California
Lynne Warner Stevenson Brigham and Women's Hospital

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 a draft copy for confidential review. On September 8, 2000, a conference call was held with our technical expert panel 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 adequately answered in the AHA/ACC guidelines, major studies were underway that would answer several more of the questions, and published data would be insufficient to reach meaningful conclusions for still others. The technical experts identified three areas where they believed significant contribution 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.

Our TEP members determined that for clinical questions 1 and 3, only the results of placebo-controlled randomized trials (RCTs) of ACE inhibitors or beta-blockers that measured outcomes of interest to patients and policymakers (including mortality, utilization, and costs) would be accepted as evidence. The TEP judged that a formal explication of a causal pathway was not needed, because numerous randomized trials had already addressed the overarching clinical

questions of the effect of the drugs on mortality and utilization. As a starting point for our research, our experts provided us with references to eight pertinent studies and the names and acronyms of the major ACE inhibitor and beta-blocker trials.

Preliminary Search

In addition to the eight reports provided by the expert panel, we searched the following databases for articles on HF treatment for the specific populations under study.

Medline, produced by the U.S. National Library of Medicine, is widely recognized as the premier source for bibliographic coverage of biomedical literature. It encompasses information form Index Medicus, Index to Dental Literature, and the Cumulative Index to Nursing and Allied Health Literature as well as other sources of literature in the areas of allied health, biological and physical sciences, humanities and information science as they relate to medicine and health care.

Healthstar, produced by the American Hospital Association, contains over one million references covering topics in hospital administration, personnel, planning, budget, accreditation, and health care delivery.

EmBase, the Excerpta Media database produced by Elsevier Science, is a major biomedical and pharmaceutical database indexing over 3,800 international journals. EMBASE currently contains over six million records, with more than 400,000 citations and abstracts added annually.

Ageline covers subjects that include aging, gerontology, health sciences, psychology, and sociology. References date from1978 to the present.

SciSearch is a database that contains all records published in Science Citation Index and additional records from about 1,000 journals listed in Current Contents. Every subject area within the board fields of science, technology, and biomedicine is included.

The **Cochrane DARE** (Database of Abstracts and Reviews of Effectiveness) contains structured abstracts of systematic reviews that have been critically appraised by reviewers at the Centre for Reviews and Dissemination, York, UK.

The specific search strategies are listed in Table 1.

Paul Shekelle, MD, and Colonel Sid Atkinson, MD, reviewed the list of retrieved titles. Of the 1,647 titles retrieved, 315 articles were deemed relevant to our undertaking and were ordered. An additional 88 articles found through mining reference lists were also ordered. Literature was tracked using Pro-Cite and Access software.

Additional Sources of Evidence

The TEP made us aware that reports of several recent studies were in press and thus would not be found through a search. Prepublication copies were provided to us.

In hopes of obtaining data on all ACE inhibitors and beta-blockers approved for HF by the Food and Drug Administration (FDA), we requested filings for each of these agents through the Freedom of Information (FOI) act. Approved ACE inhibitors included captopril, enalapril, fosinopril, lisinopril, quinipril, ramipril, and trandolapril. Approved beta-blockers included bucindolol, bisoprolol, carvedilol, and metoprolol. As discussed in the Results section, we eventually obtained data from the FDA for two studies.

Another TEP conference call was held on April 4, 2001. During this phone call, we reviewed the preliminary results of our literature search. The TEP advised us to attempt to obtain subgroup

data on all RCTs that had at least 12 weeks of followup. Since most published studies did not report on our special populations of interest, project staff sent letters to original authors requesting subgroup data (see Appendix A for sample letter). Nonrespondents were sent a reminder letter on May 8, 2001. In addition, expert panel members agreed to call or email selected nonrespondents.

Our yield from this process was poor. After mailing 62 letters, we netted four agreements (all from studies with relatively small sample sizes), 12 new contacts, 10 refusals, 32 nonresponses, and four responses categorized as other.

Based on this poor response, we modified our plan to seek subgroup data more intensively from the biggest studies through personal contacts by TEP members to the authors of those studies and through attempts to obtain individual patient data on any study that had been submitted to the FDA as part of the regulatory process. Our rationale was that we had enough resources to attempt these intensive methods on only a select number of studies and the biggest studies would provide us the greatest statistical power. We calculated that the seven largest ACE inhibitor studies enrolled 14,932 patients, whereas the remaining 19 ACE inhibitor trials enrolled an aggregate of 3,033 patients. Similarly, the five largest beta-blocker studies enrolled 12,726 patients, whereas the remaining 19 beta-blocker studies enrolled 2,938 patients. Therefore, by targeting our efforts at the largest studies, we were able to make the most effective use of our resources. However, this strategy assumes that the large and small studies are measuring the same effect.

With the assistance of our TEP members, we succeeded in obtaining the individual patient level data for TRACE from the principal investigator, Dr. Torp-Pederson. With the help of the Task Order Officer, we negotiated a confidentiality agreement with the FDA that gave us access to data submitted to the FDA as part of the regulatory process. In discussions with FDA staff, it was clear that within the constraints of time and resources, we could assess only data that had been submitted to the FDA in electronic form. FDA staff identified two studies (MERIT-HF and COPERNICUS) that had electronic data. Our confidentiality agreement required us to examine these data onsite; therefore, our quantitative analyst spent two days at the FDA working with the original data to calculate the subgroup results needed for our pooled analyses. The outcomes of our efforts to obtain subgroup data and the sources of data used in our pooled analysis are shown in Tables 2 and 3, respectively.

During the data extraction phase, it became apparent that few studies reported the relevant data stratified by age or nursing home residence. In addition, health care outcomes and health outcomes other than mortality were reported variably in the studies, making pooling less justified. For these reasons, we further restricted key questions 1 and 3 to assess only data stratified by gender, race, and diagnosis of diabetes, and to use all-cause mortality as the sole outcome of interest.

Meta-Analysis

Our principal questions for meta-analysis, as determined by our TEP, were the following:

- What is the association between treatments (ACE inhibitors or beta-blockers) and all-cause mortality for female patients, male patients, patients with diabetes, patients without diabetes, black patients, and white patients with HF?

- 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)?

Because individual studies did not enroll sufficient number of patients in the sub-populations of interest, meta-analysis is an appropriate technique to consider for these questions.

We first retrieved all articles that pertained to the eleven large placebo-controlled studies on ACE inhibitors and beta-blockers mentioned above. The SOLVD study consisted of two distinct trials on prevention and treatment respectively; thus, we considered a total of twelve studies. The same meta-analysis was done separately for the ACE inhibitor and beta-blocker sub-populations of studies, respectively.

Our outcome of interest was all-cause mortality. For studies for which both patient-level data and published statistics were available, we always chose the patient-level data over published statistics in the event of disagreement. Among the five studies for which we had patient-level data, three datasets disagreed with related publications. The differences were extremely small, never more than two patients in particular sub-populations; for example, the number of nondiabetic patients in the published article was two fewer than in the patient-level dataset. For the studies for which we had only published data, no two articles presented conflicting data about the same patient subgroup.

Relative Risks

All published reports that included the relevant patient subgroup data presented those data in the form of a two-by-two table of all-cause mortality by treatment or placebo group for each subgroup separately. If the patient-level data were available, we could construct this table directly. For example, the report of an ACE inhibitor study that stratified data by gender would provide the data in separate two-by-two tables, one for women and one for men. For each subgroup (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 extraction of data from patient-level datasets is described below.

The standard error for the log relative risk was also estimated,[5] and a 95% 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 subgroup in each study was the relative risk with its associated confidence interval. The reason for conducting the estimation on the log scale is that the variance is more stable and the errors are more symmetric in this metric.

For subgroup comparisons for which we had data from more than two studies, we pooled the logs of the relative risks across studies using the DerSimonian and Laird random effects model,[6] and back-transformed the pooled estimate to the unlogged scale to produce a pooled relative risk (e.g., for women) across all relevant studies. We also constructed a 95% confidence interval and provide a p-value for the test of whether the pooled relative risk is different from 1. We tested for heterogeneity using a chi-squared test.[7] We note that in the case when sufficient heterogeneity across studies is not found, the DerSimonian and Laird estimate of the between-study variance is 0, and the random effects estimate is the same as a fixed effects estimate, the latter incorporating

only within-study variance. Significant heterogeneity was not observed for almost all our beta-blocker pooling situations, indicating that the studies were not heterogeneous, though we acknowledge that the chi-squared test of heterogeneity has low power to detect differences across studies, and the DerSimonian and Laird estimate is only a one-step iterative method. For ACE inhibitor studies, there was substantial heterogeneity, and the random effects analysis is designed to take this into account. This meta-analysis and the ones described below were conducted in the statistical package Stata using the "meta" and associated commands.[8] The analysis just described informed us about the association between various patient characteristics (such as gender) and mortality, when association is measured on the relative risk scale. Thus, this analysis answered our first question of interest.

To answer our second question, that is, whether the association differed between sub-populations (e.g., female versus male), we needed to test whether the relative risks of the two subgroups were statistically different. We did this by constructing a test statistic equal to the ratio of relative risks (RRR), which (for the example given) equals the female relative risk divided by the male relative risk. If this test statistic differs significantly from 1, then we infer that the two subgroup relative risks 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 RRR.

For subgroup comparisons for which we had data from more than two studies, we pooled the logs of the RRRs across studies using the DerSimonian and Laird random effects model.[6] We back-transformed the pooled result to the RRR scale for interpretation, and present the pooled ratio of relative risks, its 95% confidence interval, and a p-value for the test of whether the pooled RRR is different from 1.

We note that the ratio of the pooled relative risks may not exactly equal the pooled ratio of relative risks due to the nature of the weighting. The reason for pooling of the RRRs in order to compare the relative risks, rather than pooling the relative risks separately in each subgroup and then taking the ratio, is that comparison (i.e., taking the ratio) should be done separately within each study to control for study differences.

The directions (definitions of the numerator and denominator) of the RRRs were as follows. For the effect of gender, we compared outcomes for women (numerator) versus those for men (denominator). For the effect of diabetes we compared those who had diabetes with those who did not. For the effect of race, we compared black patients to white patients if the data were stratified appropriately. If not, we compared black patients to nonblack patients, or, if necessary, we compared nonwhite patients to white patients. We conducted a sensitivity analysis as described below to assess this hierarchical approach and to determine whether the inconsistency of race classification across studies affected our conclusions.

Hazard Ratios

Followup times for outcome assessment varied across studies, and the relative risk calculations do not take this variation, or the censoring of observations, into account. Thus, we also assessed the mortality associated with ACE inhibitors and beta-blockers on the hazard ratio

scale. The hazard ratio accounts for the variable contribution made to followup by patients who dropped out of the study for whatever reason. We followed the strategy for data extraction and pooling as described in Parmar, Torri, and Stewart.[9] The majority of the studies included in our analysis 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.

For each patient subpopulation of interest, we estimated the log hazard ratio 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 calculated a ratio of hazard ratios (RHR) to compare the hazard ratios in each subgroup.

Extraction of Data from Patient-Level Datasets

We obtained data directly from patient-level datasets for five studies: CONSENSUS, COPERNICUS, MERIT-HF, SOLVD, and TRACE. For CONSENSUS, SOLVD, and TRACE, the entire patient-level files were available to us directly, and we could conduct any analyses that we wished. As described above, we constructed two-by-two tables of mortality by treatment for each subgroup of interest to estimate a relative risk and constructed a Cox proportional hazard model in SAS[10] with treatment or control as the single covariate to estimate the hazard ratio for each patient subgroup of interest.

As previously mentioned, for the other two studies, COPERNICUS and MERIT-HF, we were able to analyze the patient-level data that the FDA provided. However, we were required to analyze the data at the FDA facility. The FDA allowed one of our statisticians to have access to the data at the FDA facility in Maryland. The analyst spent one day extracting and analyzing the data for both studies. The FDA provided our analyst with a computer workstation, and the data for both studies were in SAS format. The data for each study had a table of contents in a PDF file, which, along with the drug questionnaire, was used to locate the necessary variables. Once the data were compiled in a usable format for analysis, relative risks and hazard ratios were calculated for patient sub-populations. We were able to assess all-cause mortality separately from cardiac-cause mortality.

For COPERNICUS, the randomization group, gender, race, outcome status (dead or alive at the end of the trial), and time of death or dropout (i.e., censored) variables were each in separate files and had to be merged together by patient identification number. We defined the "diabetes" subgroup as any patients whose files were identified by searching the medical history text for the root "DIABET." Two subjects who were coded as "dead" but whose files did not show dates of death were dropped from the analysis.

For MERIT-HF, an analysis file with most of our variables of interest was already available. The number of days from enrollment until death or censoring had to be calculated using either the date of death or the date of last interview.

Publication Bias

We assessed the possibility of publication bias for the studies corresponding to each drug and patient comparison subgroup by graphically evaluating a funnel plot of the individual study log relative risk and hazard ratio for symmetry resulting from the nonpublication of small, negative

studies. Because graphical evaluation can be subjective, we also conducted an adjusted rank correlation test[11] and a regression asymmetry test[12] as formal statistical tests for publication bias. We found no evidence of publication bias in any of the study subpopulations assessed.

Sensitivity Analyses

As described above, studies varied in their definitions of racial groups. For the black patient versus white patient comparison, if the researchers reported data separately for blacks and whites, we utilized those data. If such data were not available, we used data reported for black versus nonblack patients, or, as a last resort, data comparing nonwhite with white patients. For those studies that provided the data for more than one of these comparisons, we compared the relative risk and hazard ratio statistics. The results of this sensitivity analysis did not differ markedly from the results of our primary hierarchical approach. We acknowledge that this sensitivity analysis cannot assess whether the potentially different race definitions (e.g., inclusion of Hispanic black patients in the Hispanic subgroup versus the black group) had an effect. However, the sensitivity analysis did permit us to evaluate some of the effects of different race definitions and stratifications across studies.

Cost-effectiveness Analysis

At the April 4, 2001, teleconference, Paul Heidenreich, MD, proposed to the TEP that based on his analysis of the data that were suitable for cost-effectiveness modeling, the most feasible cost-effectiveness analysis would be that of the use of ACE inhibitors for asymptomatic left ventricular systolic dysfunction, rather than an analysis of the cost-effectiveness of combinations of medications, as was originally proposed. This plan was accepted by the TEP and approved by the Task Order Officer. Later, based on the findings of this analysis, a further cost-effectiveness analysis that assessed screening for left ventricular dysfunction was proposed and approved by the Task Order Officer.

Assessing Treatment of Asymptomatic Left Ventricular Dysfunction

Decision Model

We developed a decision model 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% or less but no history of HF (Figure 1). 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 HF.

Each time period (month), patients with no history of HF can remain asymptomatic, develop HF, or die. Of those patients who developed HF, we assumed 33% would be hospitalized during their initial episode.[3] Once patients develop HF, they can remain in stable HF, be hospitalized, or die during each time period. The model follows patients until each has died (or to age 120).

Health Outcomes

Published data from the SOLVD prevention trial were used to calculate rates for the development of HF and death for asymptomatic patients with and without ACE inhibitor treatment.[3] We used actual event rates during the four years of reported followup. To model outcome after four years, we used an average of the yearly event rates weighted by the number of subjects still enrolled during each year of followup. Using this method, we estimated that the yearly rate of progression to symptomatic HF would be 6.5% for patients treated with ACE inhibitors and 9.8% for those not treated. We used a similar method to determine the yearly relative risk of death (compared to the general population) for patients with asymptomatic left ventricular dysfunction who are treated (2.9) and those not treated (3.3) with ACE inhibitors.

We used data from the SOLVD treatment trial to estimate hospitalization and death rates for patients with HF treated with ACE inhibitors.[3] The data consisted of actual event rates during the four years of reported followup for the SOLVD treatment trial. To model outcome following four years of living with HF, we used an average of the annual event rates weighted by the number of subjects participating during each year of the trial. This method estimated that the yearly relative risk of death (compared to the general population) for patients with symptomatic left ventricular dysfunction was 6.5 when treated with ACE inhibitors.

To determine quality-adjusted survival, we assigned a utility value of 0.71 to each year of life for patients living with HF, based on prior studies using the time-tradeoff utility of patient preferences in HF.[13] Patients with asymptomatic left ventricular dysfunction were assumed to have a utility value of 0.87.[13] We varied these quality-of-life assumptions in sensitivity analysis (range 0.5 to 1).

Costs

We achieved a health care system perspective by using all direct costs of medical care (Table 4) including medical costs incurred due to increased survival. Because HF survivors will incur additional costs for care not associated with their HF diagnosis, we assigned all patients a yearly cost of medical care based on age-adjusted medical expenditures for residents of the United States.[14] In addition, we included the costs of hospitalization for HF, ACE inhibitor treatment, and other outpatient HF care. We adjusted all costs to 2001 dollars using the medical component of the Consumer Price Index.[15] We determined costs for hospitalization using Medicare reimbursement for DRG 127, costs for ACE inhibitor treatment using average wholesale price,[16] and outpatient HF care using prior published estimates updated to year 2001.[17] Costs and benefits were discounted at 3% per year.[18]

Assessing Screening for Reduced Left Ventricular Ejection Fraction

Screening Strategies

We modeled the expected costs of six screening strategies (Figure 2):

1. Echocardiography for all patients. Patients with an ejection fraction less than 35% are treated (ACE inhibitors) to prevent development of HF.

2. Electrocardiogram (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 test can provide one of four possible results (true positive, false positive, true negative, false negative). Only persons who are true or false positives are referred for treatment. 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.

Decision Model

A decision model was developed using EXCEL (Version 5.0, Microsoft Corporation, Redmond, WA) and DATA (Version 3.0, TreeAge Software, Boston, MA) software. We obtained the lifetime health and economic outcomes for hypothetical cohorts of 55-year-old patients with (1) depressed ejection fraction (35% 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 with heart failure but without depressed ejection fraction.

During each time period (month), patients with a low ejection fraction and without a history of HF can remain asymptomatic, develop HF, or die. Of those patients who developed HF, we assumed 33% would be hospitalized during their initial episode.[3] 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 (or until age 120). Patients without depressed ejection fraction are assumed to have an average age-specific mortality based on U.S. life table data.[19]

Test Characteristics

The sensitivity and specificity of BNP and ECG for detecting depressed left ventricular ejection fraction based on echocardiography were obtained from recently published population studies as part of the MONICA heart disease project (Table 5).[20,21] The sensitivity and specificity were used for a population at least 55 years of age with a BNP threshold of 17.9 pg/ml. For the study estimating the test characteristics of the ECG (using the MONICA population) a 12-lead tracing was considered abnormal if there were pathological Q waves, left bundle-branch block, ST-segment depression, T-wave abnormalities, left ventricular hypertrophy, atrial fibrillation, or atrial flutter per the Minnesota coding system. The age-specific prevalence of depressed ejection fraction was obtained from the same population (Table 5). Although echocardiography was the gold standard used in the above studies, the SOLVD prevention trial (for which the benefit of ACE inhibitor is based) used nuclear angiography to measure ejection fraction. The accuracy of

angiographic and echocardiographic imaging are similar;[22,23] nevertheless, we assumed that nuclear angiography was the gold standard and that echocardiography would be slightly less accurate (sensitivity of 92% and a specificity of 96%) when compared to this standard.[22]

Health Outcomes

Rates for the development of HF and death for asymptomatic patients with and without ACE inhibitor treatment were based on using published data from the SOLVD prevention trial.[3] We used actual event rates during the four years of reported followup. To model outcome after four years, we used an average of the yearly event rates weighted by the number of subjects still enrolled at each year of followup. Using this method, we estimated that the yearly rate of progression to symptomatic HF would be 6.5% for patients treated with ACE inhibitors and 9.8% for those not treated. We used a similar method to determine the yearly relative risk of death (compared to the general population) for patients with asymptomatic left ventricular dysfunction who are treated (2.9) or not treated (3.3) with ACE inhibitors.

We used SOLVD treatment trial data to estimate hospitalization and death rates for patients with HF treated with ACE inhibitors.[24] These data were actual event rates during the four years of reported followup for the SOLVD treatment trial. To model outcome following four years of living with HF, we used an average of the yearly event rates weighted by the number of subjects participating during each year of the trial. This method estimated that the yearly relative risk of death (compared to the general population) for patients with symptomatic left ventricular dysfunction was 6.5 when treated with ACE inhibitors.

To determine quality adjusted survival we assigned a utility value of 0.71 to each year of life for patients living with HF based on prior studies using the time-tradeoff utility of patient preferences in HF.[13] Asymptomatic patients were assumed to have a utility value of 0.87.[13] We varied these quality assumptions in sensitivity analysis (range 0.5 to 1).

Costs

We achieved a societal perspective by considering all costs of medical care (Table 5), including medical costs incurred due to increased survival.[18] Because HF survivors will incur additional costs for non-HF treatments, we assigned all patients a yearly age-specific cost of medical care based on medical expenditures for residents of the United States.[14] To this baseline cost, we added the costs of hospitalization for HF, ACE inhibitor treatment, and other outpatient HF care. We adjusted all costs to 2001 dollars using the medical component of the Consumer Price Index.[15] We determined costs for hospitalization using Medicare reimbursement for DRG 127, costs for ACE inhibitor treatment using average wholesale price,[16] and outpatient HF care using prior published estimates updated to year 2001.[17] Costs and benefits were discounted at 3% per year.[18] Costs of ECG and two-dimensional echocardiography were obtained from Medicare reimbursement for 2001. We assumed that Doppler and Color Doppler studies would not be performed as part of the screening echocardiogram. Because a BNP-specific reimbursement was not available, we used the commercial price of $29 per test (BioSite Inc.).

Strategy Comparisons

Because of multiple strategies, a large number of comparisons were possible. For each analysis, we first ranked the strategies by increasing effectiveness. We then compared the cost-effectiveness between the most effective strategy and the strategy that had the next-highest effectiveness. Strategies that provided less effectiveness at a higher cost were eliminated (dominance). Strategies could also be eliminated by extended dominance if a combination of two other strategies provided greater outcomes at lower costs. For example, assume the order of effectiveness of strategies is no screening< ECG screening < BNP screening.[18] If the cost-effectiveness ratio of electrocardiogram versus No Screening was greater than the cost-effectiveness ratio of BNP versus electrocardiogram, then electrocardiogram was eliminated by extended dominance. In our reporting, we excluded strategies that have been eliminated by dominance or extended dominance.

Peer Review

Identification of Peer Reviewers

At the beginning of the project, we requested nominations from several organizations for technical experts to join a panel that would advise staff throughout the project. A total of eight nominations were received for the Technical Expert Panel (TEP). In addition, experts in systematic reviews and meta-analysis were selected from a pool of experts associated with the Southern California Evidence-Based Practice Center but not involved with this project. The Project Staff, in consultation with the Task Order Officer, and Dr. Michael Rich, chairman of the TEP, suggested additional prominent cardiologists to review the report.

Peer Review Process

A copy of the draft evidence report was mailed to each peer reviewer, along with an instruction sheet for reviewing the draft evidence report (sample letter and instruction sheet included in Appendix C). The Peer Reviewers were asked to respond within three weeks. The eight of the ten peer reviewers who responded are listed below:

Stephen Gottlieb University of Maryland Medical Center
Mariell Jessup Hospital of the University of Pennsylvania
Carl Leier The Ohio State University Medical Center
Robert McNamaraJohns Hopkins University
Eric Peterson Duke Clinical Research Institute
Illeana Pina University Hospitals of Cleveland
Todd Seto The Queen's Medical Center
James Young Cleveland Clinic Foundation, Kaufman Center for Heart Failure

A copy of the draft evidence report was also mailed to the members of the Technical Expert Panel and all technical experts responded with comments. Upon receipt of all responses from the peer reviewers and technical experts, the project staff compiled a summary of the comments and

changes, and revised the draft evidence report. We forwarded all comments to the Task Order Officer for review. The peer reviewers' and technical experts' comments are included in Appendix D, together with the corresponding responses or actions taken by project staff.

Chapter 3. Results

Description of Evidence

Figure 3 displays the results of our literature search. As noted previously, our TEP provided us references for nine studies. Our library search identified another 315 articles. By reviewing the reference lists of those articles as we received them, we identified an additional 88 articles to assess. Thus, in total, 412 articles were selected. Of these, we were able to obtain 392 through the RAND library, the UCLA library, and a consulting firm that specializes in locating hard-to-find scientific journals. Of the 392 articles screened, 174 reported the results of randomized, controlled trials (RCTs) of beta-blockers or ACE inhibitors; these progressed to the Quality Review stage (see forms, Appendix B). Of these 174, 100 were rejected because they were not placebo controlled, did not report mortality outcomes, or did not report outcomes for a minimum of 12 weeks followup. This review process left 74 articles (see Evidence Tables 1 and 2).

As mentioned in Chapter 2, many of these articles described studies that appeared to include (but did not stratify according to) our populations of interest—blacks, women, and diabetics. Thus, we attempted to correspond with the authors of all studies accepted (randomized controlled trials of beta-blockers or ACE inhibitors reporting mortality data, with a minimum of 12 week followup) in an attempt to obtain patient-level data. Of 62 authors to whom we sent letters, four agreed to send us the needed data. Ten others refused, while most others either did not reply or gave us a new contact who did not reply.

Because we were unable to obtain an acceptable response to our request for additional data, we changed our focus to trying to get the data appropriately stratified by subpopulation from the "major" RCTs, which we defined as studies with sample sizes greater than 1,000 (with one exception—we also included the CONSENSUS trial, with a sample size of 253, because it was the first ACE inhibitor study to report a mortality benefit, it was widely publicized and influential in establishing ACE inhibitor therapy for heart failure, and our TEP judged that the cardiology community would expect it to be included). By repeated efforts (including personal contacts) with original authors, examination of individual patient data for some trials obtained through the FDA (as described in the Methods section), and the serendipitous publication of subgroup results during this time period, we were able to obtain the appropriate subgroup data for all the major RCTs. These placebo-controlled RCTs are briefly described below and summarized in Evidence Tables 3 and 4.

ACE Inhibitor Studies

The Acute Infarction Ramipril Efficacy (AIRE) study assessed the effect of the ACE inhibitor ramipril on 1,986 patients with clinical evidence of heart failure after having an acute myocardial infarction. The average duration of followup was 15 months. The study reported a statistically significant reduction in all cause mortality with a relative risk of 0.73 for patients treated with ramipril. [29] Some subgroup analyses were also included.

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) assessed the effect of the ACE inhibitor enalapril in 253 patients with severe heart failure (New York Heart Association class IV). The average followup period was 188 days. The study reported that at

sixth months, there was a statistically significant (40%) reduction in all-cause mortality in patients treated with enalapril.[30]

The Survival and Ventricular Enlargement Trial (SAVE) assessed the effect of the ACE inhibitor captopril in 2,231 patients with left ventricular dysfunction (defined as an ejection fraction of 40% or less, but without overt heart failure). The average followup time was 42 months. The study reported a statistically significant 19% reduction in all-cause mortality in patients treated with captopril. [31,32] Subgroup analyses were also presented. [32]

The Survival of Myocardial Infarction Long-Term Study (SMILE) assessed the effect of the ACE inhibitor Zofenopril in 1,556 patients who had an acute anterior myocardial infarction. The duration of followup was one year. The study reported a statistically significant 22% reduction in all-cause mortality for patients treated with Zofenopril.[33] The authors also reported some subgroup analyses. Although a low left ventricular ejection fraction was not a requirement for entry into this study, our TEP judged it should be included because left ventricular dysfunction is so common following anterior myocardial infarction that the enrolled population in SMILE was sufficiently similar to the other ACE inhibitor studies to justify statistical pooling. Our test of heterogeneity supported this decision.

The Studies of Left Ventricular Dysfunction (SOLVD) contained two randomized studies of the effect of the ACE inhibitor enalapril. The first study assessed the effect in 2,569 patients with New York Heart Association Class II and III heart failure and a left ventricular ejection fraction of less than or equal to 35%.[24] The average period of followup was 41.4 months. The study reported a statistically significant (16%) reduction in all-cause mortality. The second SOLVD study assessed the effect of enalapril in 4,228 patients with asymptomatic left ventricular dysfunction, defined as a left ventricular ejection fraction of 35% or less. The average followup time was 37.4 months.[34] The study reported a nonstatistically significant (8%) reduction in all-cause mortality in patients treated with captopril.

The Trandolapril Cardiac Evaluation (TRACE) study assessed the effect of the ACE inhibitor trandolapril in 1,749 patients with left ventricular systolic dysfunction (defined as an ejection fraction less than or equal to 35% with or without symptoms).[35] The patients were followed for 24–50 months. The study reported a statistically significant reduction in mortality (22%) for patients treated with Trandolapril.

Beta-Blocker Studies

The Beta-Blocker Survival Trial (BEST) assessed the effect of the beta-blocker bucindolol in 2,708 patients with New York Heart Association functional class III or IV and a left ventricular ejection fraction of 35% or lower.[36-38] The average time of followup was two years. The study reported no overall difference in mortality between treatment and placebo groups. In a subgroup analysis, nonblack patients had a statistically significant mortality benefit with a hazard ratio of 0.82.[37,38] This benefit was counterbalanced by an unexpected nonstatistically significant higher mortality rate in black patients treated with bucindolol.

The Cardiac Insufficiency Bisoprolol II Study (CIBIS-II) assessed the effect of the beta-blocker bisoprolol in 2,647 patients with New York Heart Association class III or IV heart failure and a left ventricular ejection fraction of 35% or less.[39,40] Patients were followed up for a mean of 1.3 years. The study reported a statistically significant reduction in all-cause mortality

with a hazard ratio of 0.66 for patients treated with bisoprolol. Subgroup analyses were also reported.[40]

The Carvedilol Prospective Randomized Cumulative Survival Study Group (COPERNICUS) assessed the effect of the beta-blocker carvedilol in 2,287 patients with severe heart failure equivalent to New York Heart Association class IV and left ventricular ejection fraction of less than 25%.[41] The mean period of followup was 10.4 months. The study reported a statistically significant 35% reduction in all-cause mortality for patients treated with carvedilol. Some subgroup analyses were reported.

The Metoprolol CR/XL Randomized Intervention Trial (MERIT-HF) assessed the effect of the beta-blocker metoprolol, controlled release/extended release, in 3,991 patients with New York Heart Association functional class III to IV heart failure and left ventricular ejection fraction of 40% or less.[42-44] Patients were followed for a mean of one year. The study reported a statistically significant reduction in the relative risk of mortality of 0.66 for patients treated with metoprolol. Subgroup analyses were also reported.[43,44]

The United States Carvedilol Heart Failure Trials were four separate studies that assessed the effect of the beta-blocker carvedilol in patients with mild, moderate, or severe heart failure and left ventricular ejection fraction of less than 35%.[45,46] A total of 1,094 patients were studied for six months or 12 months. A pooled analysis of the four studies reported a statistically significant reduction in mortality with a relative risk of 65% for patients treated with carvedilol. Results of the subgroup analysis were also reported.[46]

Results of Meta-Analysis

ACE Inhibitors

Gender

We were able to obtain gender-stratified data for all seven major studies to calculate the effect of ACE inhibitors on mortality. The seven studies were CONSENSUS, SAVE, the two SOLVD studies, SMILE, TRACE, and AIRE. Five of these studies had data sufficient to calculate both a RRR and a RHR. The data from SAVE could be used only in the RRR assessment, and the data from AIRE could be used only in the RHR assessment. In aggregate, these studies included 2,898 women and 11,674 men and lasted from six months (for CONSENSUS) to 42 months (SAVE). The pooled random-effects estimates from the six studies with relative risk data yielded values for men of 0.82 (95% CI: 0.74, 0.90) and for women of 0.92 (95% CI: 0.81, 1.04). These results are displayed in Table 6 and Figures 4 and 5. The corresponding pooled random effects estimates from the six studies with hazard ratio data yielded values for men of 0.76 (95% CI: 0.66, 0.87) and for women of 0.84 (95% CI: 0.72, 0.98) (Table 7 and Figures 6 and 7). The difference in effect between men and women approached statistical significance for the RRR ($p = 0.07$).

These differences between the estimates of relative risk and hazard ratios are 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, as opposed to the relative risk analysis, which included the SAVE study. This study reported a distinct but nonstatistically significant increase in mortality in women relative to men treated with captopril (RRR = 1.24).

In a subgroup analysis, studies were divided into those treating symptomatic heart failure (risk ratio analysis for CONSENSUS, SOLVD-treatment, and TRACE; hazard ratio analysis AIRE, CONSENSUS, SOLVD-treatment, and TRACE) compared with those treating for asymptomatic left ventricular systolic dysfunction (risk ratio analysis for SAVE, SOLVD-prevention, and SMILE; hazard ratio analysis 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, 1.22A, see Table 8 and Figures 8 and 9). These results are based on a pooled analysis that included 1,079 women in the symptomatic heart failure studies and 1,294 women in the asymptomatic heart failure studies. The evidence indicates that women with symptomatic heart failure benefit when treated with ACE inhibitors, although the benefit may be somewhat less that the benefit seen in men. However, the evidence calls into question whether or not women with asymptomatic left ventricular systolic dysfunction have any mortality benefit when treated with ACE inhibitors. These results are compatible with an earlier preliminary analysis of the SOLVD data.[4] Additional data are needed to answer this question. In contrast, men clearly benefit when treated with ACE inhibitors for asymptomatic left ventricular systolic dysfunction.

Some clinicians and patients find it easier to interpret relative risk data when they are converted to the "number needed to treat" (NNT). The NNT is the number of affected individuals who need to be given the treatment in question to achieve one successful outcome. In other words, in terms of this section, the NNT is the number of patients with heart failure or asymptomatic left ventricular systolic dysfunction who need to be treated with ACE inhibitors to prevent one death. Because the NNT depends on both the relative risk and the underlying risk, we have prepared a table that can be used to find the NNT for any common combination of these two variables (Table 9). We do not provide an NNT for each of our pooled estimates of effect. While the data presented in this report, in general, support an equal effect of ACE inhibitors regardless of underlying mortality risk, calculating an associated NNT requires a pooled absolute mortality risk. However, the mortality risk clearly varied across studies that enrolled patients with class IV heart failure (CONSENSUS) and studies that enrolled patients with asymptomatic left ventricular dysfunction, indicating that a pooled absolute mortality risk across studies would have no meaning.

Diabetes

Six studies stratified data by diagnosis of diabetes, permitting calculation of the differential effect of ACE inhibitors on mortality. These studies were CONSENSUS, SAVE, the two SOLVD studies, SMILE, and TRACE. 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, the SAVE 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) whereas 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 data are presented in Tables 10 and 11 and Figures 10–13. We interpret these results as indicating that both patients with diabetes and patients

without diabetes achieve reductions in mortality when treated with ACE inhibitors for heart failure.

Race

Three studies provided data stratified by patient race to assess the effects of ACE inhibitors on mortality. The studies with appreciable numbers of black patients were SAVE and the two SOLVD studies. The remaining ACE inhibitor studies (AIRE, CONSENSUS, SMILE, and TRACE) were conducted primarily in Scandinavian and European countries and did not include substantial numbers of black patients. SAVE did not present data that allowed us to calculate the hazard ratios, which left only two studies (the SOLVD studies), an insufficient number 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 are presented in Tables 12 and 13 and Figures 14 and 15. We interpret these data as indicating that there is no evidence that black patients achieve lesser or greater reductions in mortality than white patients when treated with ACE inhibitors for heart failure. Whereas the relative risk reduction in black patients did not achieve conventional levels 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 differ from each other statistically. Therefore, the most likely explanation for the lack of statistical significance in the estimate for black patients is the much smaller sample size, which increases the standard error and 95% confidence intervals. These results are consistent with the analysis by the SOLVD investigators that there was not a lesser reduction in mortality among black compared to white patients in the SOLVD studies (these investigators did, however, report a difference in hospitalization rate in black patients compared to white patients).[34]

Beta-Blockers

Gender

Five studies on the effects of beta-blocker treatment on mortality stratified data by gender. The studies were CIBIS II, COPERNICUS, MERIT-HF, BEST, and US Carvedilol. The CIBIS II study contributed data only to the relative risk analysis. Bucindolol, which was the beta-blocker evaluated in BEST, was judged by our TEP to be sufficiently different in action from the other beta-blockers that the results of the BEST study should not be pooled with those of the other studies. In aggregate, the pooled studies included 2,134 women and 7,885 men. Both analyses yielded similar results. The random-effects pooled estimate for the relative risk of mortality for women was 0.63 (95% CI: 0.44, 0.91), whereas 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). These data are presented in Tables 14 and 15 and Figures 16 -19. Our interpretation of these data is that women and men with symptomatic heart failure have reduced mortality when treated with beta-blockers.

Diabetes

Three studies stratified data by diagnosis of diabetes, permitting calculation of the differential effect of beta-blockers on mortality. In aggregate, these studies included 1,883 patients with diabetes and 7,042 patients without diabetes. The only pooled estimates that were possible were the relative risks, which 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% confidence interval was very broad. These data are presented in Tables 16 and 17 and Figures 20 and 21. Our interpretation of these data is that patients with diabetes and HF have reduced mortality when treated with beta-blockers. It is possible that the relative reduction in mortality may be less for patients with diabetes than for those without diabetes, but since the absolute risk of mortality is so much greater in diabetic patients, the absolute risk reduction is almost certainly greater for diabetic than for nondiabetic HF patients treated with beta-blockers.

Race

We were able to obtain race-stratified data to assess the effects of beta-blocker treatment on mortality in four studies. These studies were BEST, COPERNICUS, MERIT-HF and US Carvedilol. As mentioned above, BEST was judged to be clinically dissimilar to the other studies and was not included in the pooled analysis. The CIBIS-II 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 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 black patients was 0.67 (95% CI: 0.39, 1.16), whereas for white patients, 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. These data are displayed in Tables 18 and 19 and Figures 22–25.

In contrast, black patients in the BEST study had a statistically significant difference in mortality compared to white patients when treated with bucindolol. In fact, the relative risk and hazard ratio for mortality exceeded 1 for black patients (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. Although the results for black patients were not statistically significant compared to placebo, because the point estimates of effect were similar to white patients, we judge the most likely reason for this finding to be the much smaller sample size. In contrast, bucindolol was associated with worse mortality outcomes in black patients than in white patients, and may actually increase mortality in blacks. Additional data are needed in this area.

Results of Cost-Effectiveness Analysis

Assessing Treatment of Asymptomatic Left Ventricular Dysfunction

Model Validation

For the base-case analysis of a 55-year-old man with an ejection fraction less than 40% and no history of symptomatic heart failure, the model predicted an average life expectancy without ACE inhibitor treatment of 8.1 years (Figure 26) and a 57% five-year morbidity and mortality rate (Figure 27). These results are similar to the findings of the SOLVD prevention study.[3]

Base-Case Results

Treatment with ACE inhibitors improved survival and quality-adjusted survival by eight months compared to no treatment (Table 20). The lifetime cost of care was $3,718 greater for patients treated with ACE inhibitors with a cost per life year gained of $5,802 and cost per QALY gained of $5,644 compared to no treatment (Table 20).

Sensitivity Analyses

We tested the robustness of our base-case findings by varying each of the assumptions in Table 4 over the ranges listed. 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. We describe a subset of the variables tested in sensitivity analyses in the following paragraphs.

Patient Age. For the base-case analysis, we assumed an age of 55 years. For older age groups, both the cost and benefit of treatment with ACE inhibitors decreased. For an 80-year-old person, the marginal cost-effectiveness was $6,650 per QALY, which was only slightly higher than $4,666 per QALY for a 50-year old person.

Risk of Death with Heart Failure. Our base-case analysis assumed that the risk of death for patients with heart failure treated with ACE inhibitors was 6.5 times greater than the risk of death for the U.S. age-adjusted population.[3] If we assumed a lower risk of death (relative risk 2.0), both costs and life expectancy increased, but the cost-effectiveness ratio remained favorable ($4,093 per QALY).

Reduction in Heart Failure Incidence. If the reduction in heart failure incidence with ACE inhibitor treatment was only half of the effect observed in the SOLVD trial, treatment cost remained less than $10,000 per QALY gained. Even when we assumed no reduction in mortality for asymptomatic patients treated with ACE inhibitors, treatment had to reduce the yearly probability of developing symptomatic heart failure from 9.8% (untreated) to only 9.5% (3% relative risk reduction) for the cost-effectiveness ratio to drop below $100,000 per QALY gained, and to 9.1% (7% relative risk reduction) for the cost-effectiveness ratio to drop below $50,000 per QALY gained.

Reduction in Risk of Death for Asymptomatic Patients. In the base case, we assumed a slight improvement in survival with ACE inhibitor treatment, independent of the development of

heart failure. Even when we removed this assumption, the cost-effectiveness of ACE inhibitor treatment remained only $6,474 per QALY (Figure 28).

Probability of Hospitalization if Symptomatic. We assumed that 11% of patients with heart failure would he hospitalized each year. If 15% were hospitalized each year, the cost per QALY gained dropped to $5,272. Even if hospitalizations for heart failure patients were completely eliminated by ACE inhibitor treatment, preventing heart failure ($6,539 per QALY gained) still remained cost-effective because heart failure also increases outpatient costs and worsens quality of life. Our findings were also insensitive to the probability of being hospitalized with the first episode of symptomatic heart failure.

Costs. The cost-effectiveness of ACE inhibitors was insensitive to the cost of treatment. If the cost of treatment was $5 per day, the cost-effectiveness ratio remained less than $10,000 per QALY (Figure 29), and even if the cost of the ACE inhibitor were 0, treatment would not be cost saving because the improvement in survival (both before and after the development of symptoms) simply delays medical costs to older ages. If ACE inhibitors did not affect survival for asymptomatic patients with low ejection fraction, overall medical costs would be lower if the cost of ACE inhibitor treatment was less than $75 per year.

The cost of hospitalization had little effect on cost-effectiveness. Eliminating all hospitalizations did not raise the cost-effectiveness threshold above $7,400 per QALY gained. In addition, the cost of outpatient management did not affect our results. The cost per QALY gained ranged from $5,920 (if the annual outpatient cost was $200) to $5,306 (if the cost was $800). The discount rate also had little effect on the results. A discount rate of 0% resulted in $5,592 per QALY gained, compared to $5,776 per life year gained if the discount rate was 6%.

Quality of Life. We evaluated the effect of various utility values for living with heart failure on the cost-effectiveness of prevention with ACE inhibitors. In the base case, we assumed that quality-of-life utility would drop from 0.865 when asymptomatic to 0.71 when symptomatic (difference of 0.155), based on time-tradeoff utilities from the Beaver Dam Study.[13]

Similar results were found when we used the visual analog scale data from the SOLVD trial. In that study, the patients with asymptomatic low ejection fraction rated their quality of life at 0.68, compared with 0.60 for patients with symptoms. Using their values, we found the cost-effectiveness of ACE inhibitor treatment to be only $7,598 per QALY gained.

Assessing Screening for Reduced Left Ventricular Ejection Fraction

Base-Case Results

For a population of asymptomatic individuals, age 55 (prevalence of low ejection fraction 2.7%), 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 (Table 21). If quality of life is ignored, BNP screening costs $19,000 per life-year gained compared to no screening. The number needed to screen was 77 to gain one 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 (extended dominance), this strategy was eliminated as a possible screening option for the base-case cohort. BNP screening

demonstrated extended dominance over ECG screening, because the incremental cost-effectiveness ratio for BNP compared to ECG screening was less than the ratio for ECG screening compared to no screening. Willingness to pay for the benefits of ECG screening ensures a willingness to pay for the extra benefits of BNP screening. 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. The ECG- and BNP-only strategies are not discussed further. All future references to BNP or ECG screening assumes that abnormal tests are followed by echocardiography.

Sensitivity Analyses

We tested the robustness of our base-case findings by varying each of the assumptions in Table 5 over the ranges listed. The decision to screen is primarily affected by the prevalence of low ejection fraction and the accuracy of the screening tests. The model was only mildly sensitive to the costs of screening, including echocardiography and BNP testing. The results of the sensitivity analysis are detailed here.

Prevalence of Depressed Left Ventricular Function. For the base-case analysis, we assumed an asymptomatic population of 55 and older would be screened. The prevalence of depressed ejection fraction will be higher in older populations and groups with established cardiovascular disease (Table 22). If the prevalence of low ejection fraction is at least 0.4%, the incremental cost-effectiveness of BNP screening is less than $100,000 per QALY gained (Figure 30). For the cost-effectiveness ratio with BNP screening to be less than $50,000 per QALY gained, the prevalence must be greater than 0.8%; to be under $20,000 per QALY gained, the prevalence must be 2.5%. BNP screening is never cost *saving,* even at 100% prevalence of disease, because treatment of asymptomatic patients with ACE inhibitors is more expensive than not treating these patients.

Test Characteristics of BNP. Past population studies of patients over 55 have indicated that the sensitivity of BNP (using a cut-off of 17.9 pg/ml) for depressed ejection fraction is 89%. If the sensitivity is actually below 65%, ECG screening is preferred (sensitivity 60%, specificity 82%, Figure 31). The specificity of BNP testing for detecting depressed left ventricular function is estimated to be 71%. Even if the specificity is 50%, the cost per QALY gained would be less than $50,000, compared to screening with the ECG (Figure 32). If the specificity is at least 70%, the ECG strategy is no longer viable (eliminated by extended dominance).

Past studies have used different cut-points for an abnormal BNP test, based on the appearance of the receiver-operator characteristics curve. However, the particular cutoff chosen may not be optimal in terms of cost-effectiveness. Using various sensitivity and specificity combinations from the MONICA patient population,[20] we found that both cost of care and quality-adjusted survival improve as sensitivity increases and specificity decreases. If society is willing to pay $100,000 per QALY gained, using a low BNP threshold (24ng/ml) that produces a sensitivity near 96% with specificity near 65% is optimal. However, if society will pay only $20,000 per QALY gained, then a BNP threshold slightly above 18ng/ml (sensitivity 72%, specificity 90%) is optimal.

Cost of Testing. BNP testing remained the optimal strategy over a wide range of test costs (Figure 33). The cost per QALY gained with BNP screening (compared to ECG screening) remained less than $50,000 as long as the cost of the BNP test was less than $120.

The Medicare reimbursement for two-dimensional echocardiography has been dropping (without adjustment for inflation) in an attempt to better match actual costs of delivering treatment, as estimated by the Center for Medicare and Medicaid Services (formerly the Health Care Financing Administration). Significant disagreement exists between specialty societies and Medicare regarding the actual cost of an echocardiogram. However, even if echocardiography costs were as high as $1,000, BNP screening would still cost only $37,600 per QALY gained compared to ECG screening, and ECG screening would cost $34,200 per QALY gained compared to no screening.

ECG is similar in price to BNP testing. Therefore, the decision to use one over the other is based on the differences in test characteristics.

Impact of ACE Inhibitors for Patients with Reduced Ejection Fraction. In the base case, we estimated an increase in 0.6 QALYs for patients with low ejection fraction who take ACE inhibitors while asymptomatic compared to those who initiate treatment when they develop heart failure. If the gain in QALYs with preventive ACE inhibitor use is at least 0.3, screening with BNP costs less than $50,000 per QALY gained, compared to no screening (Figure 34).

ACE Inhibitor Use in Healthy Patients. We assumed a small decrement in quality-adjusted survival (0.001 years or 0.37 days) each year to account for potential side effects of ACE inhibitor treatment. Because no quality-of-life studies of ACE inhibitor use in healthy patients are available, the negative health impact of taking unneeded medication is unknown. However, our findings were similar over a wide range of quality-of-life decrements for ACE inhibitor treatment. The cost-effectiveness of BNP screening (compared to no screening; ECG screening was eliminated by extended dominance) ranged from $18,200 per QALY gained (for no decrease in quality adjusted survival) to $20,300 per QALY gained (for a three-day reduction per year in quality-adjusted survival) for normal patients taking ACE inhibitors.

Chapter 4. Limitations

The meta-analyses have several potential limitations:

- An important limitation, common to many such meta-analyses, is the differential quality of the original studies. We cannot adjust for any inherent biases in the individual studies. However, to mitigate this limitation, we included studies that were double-blind randomized controlled trials and used all-cause mortality as the outcome. These design features help protect against some of the more important biases.

- We restricted attention to the large trials on ACE inhibitors and beta-blockers due to resource constraints. By excluding smaller trials, we may have limited our generalizability and our ability to investigate heterogeneity in treatment effects. We did observe little to no evidence of publication bias among the large trials via visual inspection or formal testing and, given the notable nature of such trials, are fairly confident we did not miss a similar trial in our extensive search.

- Between-study heterogeneity was observed, especially among the ACE inhibitor studies. Although the random-effects model is designed to take this extra variability into account in the estimation of the standard errors and generally widens the confidence interval for the pooled estimate, this model does not explain the heterogeneity. In fact, significant between-study heterogeneity should lead us to interpret a pooled result with caution.

- We conducted a meta-analysis of study summary statistics (relative risks, etc.), rather than a patient-level data analysis due to the fact we could not obtain patient-level data for all trials in a timely and efficient manner. This approach limited us in two ways. First, we were unable to estimate hazard ratios for all subgroups of interest and had to rely on relative risks for some studies. The latter statistic does not adjust for differential followup intervals across studies. Second, we cannot investigate interactions between patient-level characteristics that might mitigate the treatment effect, nor can we adjust for these effects in our estimates. For example, suppose blacks are more likely to have hypertension than whites, and the treatment works less well for patients with hypertension than for those who do not have hypertension. We may conclude that the treatment works less well for blacks than whites when actually if we had controlled for hypertension status, we would not have seen differences between the two racial subgroups. By ignoring the effect of hypertension, we incorrectly attribute its association with treatment to race. A patient-level data analysis would have allowed this adjustment, had data on important confounders been collected.

- Studies did differ in their definition of racial groups. A sensitivity analysis that we conducted to try to determine whether this variability affected our conclusions did not show different results using different definitions.

The cost-effectiveness analyses have several potential limitations:

- We relied on the SOLVD prevention trial to determine the impact of ACE inhibitors on patients with asymptomatic left ventricular dysfunction. Although this is the best data source available, the SOLVD patients were not randomly selected from the population. It is possible that randomly selected patients with reduced left ventricular function may show less benefit with ACE inhibitors.

- Our analysis did not include the potential impact of beta-blockers in the base case, because these agents have not yet been evaluated in randomized trials of asymptomatic patients. If beta-blockers have an incremental benefit over ACE inhibitors in this population, the cost-effectiveness of screening will likely improve, assuming beta-blocker treatment is cost-effective for heart failure patients.

- We limited our analysis of BNP to screening asymptomatic subjects. Our study did not examine the appropriate use of BNP to adjust medications (e.g., dose of diuretics, use of digoxin) for patients with heart failure.

- Our study did not specifically model other tests (biopsy, cardiac catheterization) and treatments (revascularization) that may result from the knowledge of depressed left ventricular function, because there is no accepted standard of care with additional testing or treatments (other than ACE inhibitors and possibly beta-blockers) for asymptomatic patients with reduced ejection fraction. Any additional testing such as screening for coronary artery disease should be evaluated with a separate cost-effectiveness analysis.

- Our cost-effectiveness analysis did not distinguish between patient subgroups. If ACE inhibitors are more or less effective in men or women, the cost-effectiveness of treatment (and screening for depressed ejection fraction) will vary by gender. Additional studies are needed to determine which patient groups have a high enough prevalence of depressed left ventricular function (> 1%) to make screening cost-effective.

Chapter 5. Conclusions

We believe several conclusions can be drawn from this evidence report. For the purposes of discussion, we divide these conclusions into those that pertain to methodological considerations, those that pertain to clinical issues, and those that pertain to the cost-effectiveness analysis.

Methodological Conclusions

1. A large enough number of placebo-controlled, randomized trials of ACE inhibitors or beta-blockers have been conducted to assess their efficacy for the prevention and treatment of heart failure.

2. Few of these studies have reported data stratified by patient subpopulations of interest to clinicians.

3. Obtaining these subgroup data by attempting to contact authors of the original studies is both time consuming and not particularly successful. Attempts on the scale used to generate this report are not within the time– and resource–constraints of typical AHRQ evidence reports.

4. Obtaining subpopulation data by inspecting data submitted to the FDA is a potentially fruitful area but only to the extent that the data are already in electronic form. Paper-based records are too difficult to retrieve and too voluminous to review efficiently.

5. Two Evidence-Based Practice Centers can successfully collaborate on the same evidence report. In this case, the cost-effectiveness analyses were performed at the Stanford-UCSF Evidence Based Practice Center.

Clinical Conclusions

1. For most of the subpopulations assessed in our meta-analysis, our results are reassuring in that we found evidence supporting beneficial reductions in all-cause mortality with the use of beta-blockers in men and women, the use of ACE inhibitors in black and white patients, and the use of either drug in patients with diabetes.

2. We did, however, find evidence suggesting 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 is needed to analyze the effect of ACE inhibitors in women with asymptomatic left ventricular dysfunction.

3. We also found conflicting evidence regarding the effect of beta-blocker use in black patients. For three of the beta-blocker studies, the pooled estimate of effect suggested that black patients and white patients have similar reductions in all-cause mortality when treated with beta-blockers. However, one study, which was unique in that it assessed the beta-blocker bucindolol, reported a statistically significant adverse effect on mortality in blacks relative to whites, even suggesting that use of bucindolol caused harm. These results suggest that all beta-blockers cannot be assumed to have similar effects.

Cost-Effectiveness Conclusions

1. We found that treatment of asymptomatic left ventricular dysfunction with ACE inhibitors was very cost-effective under virtually all assumptions, with typical costs per QALY gained of between $5,000–$10,000, which makes this treatment much more cost-effective than many other treatments considered standard medical practice.

2. The analysis of the cost-effectiveness of screening showed that screening with brain natriuretic peptide followed by echocardiography in a cohort of asymptomatic individuals aged 55 was also cost-effective compared with the costs of other therapies 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 in order to gain one year of additional life.

3. These results were only modestly sensitive to cost and were most sensitive to the prevalence of asymptomatic decreased left ventricular ejection fraction. When the prevalence falls below about 1%, a strategy of screening becomes less cost-effective than accepted thresholds for cost-effective care.

Chapter 6. Future Research

The findings of this evidence report suggest several important future research studies. The first and most important would be for additional data to support or refute the evidence that different beta-blockers may have different effects on all-cause mortality in black patients. We do not think it likely that additional analysis of existing data will be able to conclusively settle this issue. New placebo-controlled randomized clinical trials of beta-blocker therapy in black patients are likely the only way to definitively answer this question. Future studies of existing or new beta-blocker drugs for heart failure should 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.

A second area for future research is further assessment of the effect of ACE inhibitors in women with heart failure, particularly the effect on women with asymptomatic left ventricular dysfunction. It may be possible to answer this question by a more complete assessment of existing data from randomized clinical trials. This would require an individual patient data meta-analysis, which in turn would require obtaining individual patient data from all of the randomized trials. While such an effort would be expensive, it may be less expensive and more ethical than mounting a new clinical trial designed to answer this question.

Additionally, other outcomes of interest, including cardiac mortality, symptoms, and health care utilization, should be examined for all patient subpopulations. Individual patient-level data from the major RCTs may be sufficient to answer these and other original key questions regarding more patient subpopulations (the aged and those with renal failure).

An additional implication of our finding is that inadequate attention has been paid to enrolling sufficient numbers of patients in important clinical subpopulations in randomized trials. Such attention would make meta-analyses like those contained in this report unnecessary.

If our findings of differential efficacy are sustained, additional research aimed at identifying 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 gender 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. Yet another area for future research is empirical tests of our conclusions from our cost-effectiveness analyses.

Additional studies are needed to determine the true prevalence of asymptomatic left ventricular dysfunction and to determine the 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%). In addition, a study evaluating the health and economic outcomes of screening asymptomatic patient with BNP is warranted.

References

1. American Heart Association. 1998 Heart and stroke statistical update. Dallas: American Heart Association; 1997.

2. Materson BJ, Reda DG, Cushman WC, et al. Single-drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo. N Engl J Med 1993;328:914.

3. Yusuf S, Nicklas JM, Timmis G, et al. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. N Engl J Med 1992;327:685-691.

4. Limacher MC, Yusuf S. Cardiovascular health and disease in women. In: Wenger, Speroff, Packard (eds): Proceedings of an NHLBI Conference. Darien:LeJacq; 1993.

5. Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincott-Raven Publishers; 1998.

6. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-188.

7. Hedges LV, Olkin I. Statistical methods for meta-analysis. San Diego: Academic Press, Inc.; 1985.

8. Stata Corporation. Stata Statistical Software. Release 7.0. College Station: Stata Corporation; 2001.

9. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815-2834.

10. SAS Institute, Inc. SAS/STAT. Cary, NC: SAS Institute, Inc.; 1999.

11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634.

12. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-1101.

13. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Med Decis Making 1993;13:89-102.

14. U.S. Bureau of the Census. Statistical abstract of the United States. U.S. Census Bureau: Washington;2000.

15. Bureau of Labor Statistics. Consumer price index. http://www.bls.gov/cpi/home.htm.

16. AAUP policy documents and reports (The Redbook). Baltimore: Johns Hopkins University Press; 2001.

17. Paul SD, Kuntz KM, Eagle KA, Weinstein MC. Costs and effectiveness of angiotensin converting enzyme inhibition in patients with congestive heart failure. Arch Intern Med 1994;154:1143-9.

18. Gold M, Siegel J, Russel L, Weinstein M (eds.). Cost Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.

19. National Center for Health Statistics. United States life tables, 1998 (PHS 2000-1120). Atlanta: Centers for Disease Control and Prevention; 2000.

20. McDonagh TA, Robb SD. Murdoch DR, Morton JJ, Ford I, Morrison, CE, Tunstall-Pedoe H, McMurray JJV, Dargie HJ. N Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998;351:9-13.

21. McDonagh TA, Morrison CE, Lawrence A, et al. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. Lancet 1997; 350:829-33.

22. Naik MM, Diamond GA, Pai T, et al. Correspondence of left ventricular ejection fraction determinations from two-dimensional echocardiography, radionuclide angiography and contrast cineangiography. J Am Coll Cardiol 1995;25:937-42.

23. Schiller NB, Acquatella H, Ports TA, et al. Left ventricular volume from paired biplane two-dimensional echocardiography. Circulation 1979;60:547-55.

24. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

25. National Center for Health Statistics. Vital Statistics of the United States: Mortality. Atlanta: Centers for Disease Control and Prevention; 1991.

26. American Heart Association. Heart and stroke statistical update. Dallas: American Heart Association; 2000.

27. Glick H, Cook J, Kinosian B, et al. Costs and effects of enalapril therapy in patients with symptomatic heart failure: an economic analysis of the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial. J Cardiac Failure 1995;1:371-380.

28. Cook JR, Glick HA, Gerth W, et al. The cost and cardioprotective effects of enalapril in hypertensive patients with left ventricular dysfunction. Am J Hypertens 1998;11:1433-41.

29. Ball SG, Hall AS, Mackintosh AF, et al. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. the Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993;342 (8875):821-8.

30. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.

31. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327 (10);669-77.

32. Moye LA, Pfeffer MA, Wun CC, et al. Uniformity of captopril benefit in the SAVE study: subgroup analysis. Eur Heart J 1994;15:2-8.

33. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. N Engl J Med 1995;332:80-85.

34. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Eng J Med 2001;344:1351-7.

35. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333(25):1670-6.

36. The Beta-Blocker Evaluation of Survival Trial Investigators (BEST): a trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344:1659-67.

37. Eichhorn EJ, Domanski MJ, Adams K, et al. Effect of beta-blockade on mortality in African-Americans: the beta-blocker evaluation of survival trial. Circulation 2000;102(suppl 2):18.

38. Plehn JF, Krause-Steinrauf H, Anand IS, et al. Effect of race on cause-specific cardiovascular mortality in BEST. Circulation 2000;102(suppl 2):18.

39. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9-13.

40. Erdmann E, Lechat P, Verkenne P, Wiemann H. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. Euro J Heart Failure 2001;3:469-479.

41. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.

42. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001-2007.

43. Wedel H, DeMets D, Deedwania P, et al. Challenges of subgroup analyses in multinational clinical trials: experiences from the MERIT-HR trial. Am Heart J 2001;142:502-11.

44. Ghali JK, Pina IL, Gottlieb SS, et al. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). Circulation 2002;105:1585-91.

45. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334:1349-55.

46. Yancy CW, Fowler MB, Colucci WS, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. N Engl J Med 2001;344:1358-65.

Bibliography

Accepted Articles

Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med.* 1995;332(2):80-85.

Anderson JL, Lutz JR, Gilbert EM, Sorensen SG, Yanowitz FG, Menlove RL, et al. A randomized trial of low-dose beta-blockade therapy for idiopathic dilated cardiomyopathy. *Am J Cardio.* 1985;55(4) p471-5.

Andersson B, Hamm C, Persson S, Wikstrom G, Sinagra G, Hjalmarson A, et al. Improved exercise hemodynamic status in dilated cardiomyopathy after beta-adrenergic blockade treatment. *J Am Coll Cardiol*. 1994;23(6):1397-404.

Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Australia/New Zealand Heart Failure Research Collaborative Group *Lancet.* 1997;349(9049) p375-80.

Ball SG, Hall AS, Mackintosh AF, et al. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators *Lancet.* 1993;342(8875) p821-8.

Barabino A, Galbariggi G, Pizzorni C, et al. Comparative effects of long-term therapy with captopril and ibopamine in chronic congestive heart failure in old patients. *Cardiology*. 1991;78:289-296.

Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation.* 1996;94:2807-2816.

Bristow MR, O'Connell JB, Gilbert EM, French WJ, Leatherman G, Kantrowitz NE, et al. Dose-response of chronic beta-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. Bucindolol Investigators. *Circulation.* 1994;89(4) p1632-42.

Brown E J Jr, Chew PH, MacLean A, Gelperin K, Ilgenfritz JP, Blumenthal M. Effects of fosinopril on exercise tolerance and clinical deterioration in patients with chronic congestive heart failure not taking digitalis. Fosinopril Heart Failure Study Group. *Am J Cardio*. 1995;75(8) p596-600.

Bulpitt CJ, Fletcher AE, Dossegger L, Neiss A, Nielsen T, Viergutz S. Quality of life in chronic heart failure: cilazapril and captopril versus placebo. Cilazapril-Captopril Multicentre Group. *Heart.* 1998;79(6):593-8.

Bussmann WD, Storger H, Hadler D, et al. Long-term treatment of severe chronic heart failure with captopril: a double-blind randomized, placebo-controlled long-term study. *J Cardiovasc Pharmacol*. 1987;9(suppl. 2):S50-S60.

Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. The Captopril-Digoxin Multicenter Research Group. *JAMA.* 1988;259(4):539-44.

Chalmers JP, West MJ, Cyran J, De La Torre D, Englert M, Kramar M, et al. Placebo-controlled study of lisinopril in congestive heart failure: a multicentre study. *J Cardiovasc Pharmacol.* 1987;9 Suppl 3 pS89-97.

CIBIS Investigators and Committees A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS).. *Circulation.* 1994;90(4):1765-73.

CIBIS-II: The Cardiac Insufficiency Bisoprolol Study II: a randomised trial. *Lancet.* 1999;353(9146):9-13.

Cice G, Tagliamonte E, Ferrara L, Iacono A. Efficacy of carvedilol on complex ventricular arrhythmias in dilated cardiomyopathy: double-blind, randomized, placebo-controlled study *Eur Heart J.* 2000;21(15):1259-64.

Cleland JG, Erhardt L, Murray G, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators *Eur Heart J.* 1997;18(1):41-51.

Cohn JN, Fowler MB, Bristow MR, Colucci WS, Gilbert EM, Kinhal V, et al. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. *Journal of Cardiac Failure.* 1997;3(3) p173-9.

Colucci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation.* 1996;94:280-2806.

The CONSENSUS Trial Study Group Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med.* 1987;316(23):1429-35

Creager MA, Massie BM, Fascon DP, et al. Acute and long-term effects of Enalapril on the cardiovascular response to exercise and exercise tolerance in patients with congestive heart failure. *JACC.* 1985;6:163-70.

Cucchini F, Compostella L, Papalia D, de Domenico R, Iavernaro A, Zeppellini R [Chronic treatment of dilated cardiomyopathy by beta blocking agents. Clinical and hemodynamic follow-up]: <Original> Trattamento cronico della cardiomiopatia dilatativa con betabloccanti. Controllo clinico ed emodinamico a distanza. *Giornale Italiano Di Cardiologia.* 1988;18(10) p835-42.

Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Effects of carvedilol on left ventricular regional wall motion in patients with heart failure caused by ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. *J Card Fail.* 2000;6(1):11-8.

Eichhorn EJ, Domanski MJ, Adams K, et al. Effect of beta-blockade on mortality in African-Americans: The beta-blocker evaluation of survival trial. *Circulation.* 2000;102 (suppl 2)(18).

Eichhorn EJ, Heesch CM, Barnett JH, Alvarez LG, Fass SM, Grayburn PA, et al. Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol.* 1994;24(5):1310-20.

Erdmann E, Lechat P, Verkenne P, Wiemann H. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *Euro J Heart Failure.* 2001;3:469-479.

Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Eng J Med.* 2001;344(18):1351-7.

Exner DV, Dries DL, Domanski MJ, et al. Enalapril therapy and outcome in Black versus White patients enrolled in the studies of left ventricular dysfunction. *Circulation.* 2000;102(18).

Fisher ML, Gottlieb SS, Plotnick GD, Greenberg NL, Patten RD, Bennett SK, et al. Beneficial effects of metoprolol in heart failure associated with coronary artery disease: a randomized trial. *J Am Coll Cardiol.* 1994;23(4) p943-50.

Genth-Zotz S, Zotz RJ, Sigmund M, Hanrath P, Hartmann D, Bohm M, et al. MIC trial: metoprolol in patients with mild to moderate heart failure: effects on ventricular function and cardiopulmonary exercise testing. *Eur J Heart Fail.* 2000;2(2) p175-81.

Ghose JC, Chakraborty S, Mondal M, Bhandari B. Effect of vasodilator therapy on mortality in chronic congestive heart failure. *Journal of the Association of Physicians of India.* 1993;41(5) p269-71.

Gilbert EM, Anderson JL, Deitchman D, Yanowitz FG, O'Connell JB, Renlund DG, et al. Long-term beta-blocker vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: a double-blind, randomized study of bucindolol versus placebo. *Am J Med.* 1990;88(3) p223-9.

Giles TD, for Lisinopril Chronic Heart Failure Group. Lisinopril treatment of congestive heart failure-results of a placebo controlled trial. *Circulation*. 1990;82(suppl 4):III-323.

Gundersen T, Wiklund I, Swedberg K, Amtorp O, Remes J, Nilsson B. Effects of 12 weeks of ramipril treatment on the quality of life in patients with moderate congestive heart failure: results of a placebo-controlled trial. Ramipril Study Group. *Cardiovascular Drugs and Therapy*. 1995;9(4) p589-94.

Gustafsson I, Torppedersen C, Kober L, Gustafsson F, Hildebrandt P. Effect of the angiotensin-converting enzyme inhibitor trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after acute myocardial infarction. *J Am Coll Cardiol*. 1999;34(N1. JUL):83-89.

Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Acute Infarction Ramipril Efficacy *Lancet*. 1997;349(9064) p1493-7.

Herlitz J, Waagstein F, Lindqvist J, Swedberg K, Hjalmarson A. Effect of metoprolol on the prognosis for patients with suspected acute myocardial infarction and indirect signs of congestive heart failure (a subgroup analysis of the Goteborg Metoprolol Trial). *Am J Cardio*. 1997;80(9B) p40J-44J.

Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA*. 2000;283(10) p1295-302.

Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169):2001-2007.

Jerie P, Kremer HJ, Uhlir O, Widimsky J. [A Czech and Slovak interventional study of spirapril (the CASSIS study). A randomized, double-blind, multicenter, placebo-controlled study in chronic heart failure]: <Original> Ceska a slovenska intervencni studie se spiraprilem (studie CASSIS). Randomizovana, dvojiteslepa, multicentricka studie, kontrolovana aktivne i placebem chronickeho srdecniho selhani. Za resitele studie CASSIS. *Vnitrni Lekarstvi*. 1997;43(6) p351-8.

Keren G, Pardes A, Eschar Y, Koifman B, Scherez J, Geleranter I, et al. One-year clinical and echocardiographic follow-up of patients with congestive cardiomyopathy treated with captopril compared to placebo. *Israel Journal of Medical Sciences*. 1994;30(1) p90-8.

Kjekshus J, Swedberg K. Enalapril for congestive heart failure. *Am J Cardio*. 1989;63(8) p26D-32D.

Kleber FX, Laube A, Osterkorn K, et al. Captopril in mild to moderate heart failure after 18 months: effects on morbidity and mortality. *JACC*. 1987;9:42A (Abstr).

Kleber FX, Niemoller L, Doering W. Impact of converting enzyme inhibition on progression of chronic heart failure: results of the Munich Mild Heart Failure Trial. *British Heart Journal*. 1992;67(4) p289-96.

Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med*. 1995;333(25) p1670-6.

Krum H, Sackner-Bernstein JD, Goldsmith RL, Kukin ML, Schwartz B, Penn J, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation*. 1995;92(6) p1499-506.

Magnani B. Converting enzyme inhibition and heart failure. *Am J Med*. 1988;84(3A) p87-91.

Magnani B, Magelli C. Captopril in mild heart failure: pre liminary observations of a long-term, double-blind, placebo-controlled multicentre trial. *Postgraduate Medical Journal*. 1986;62 Suppl 1 p153-8.

Moye LA, Pfeffer MA, Wun CC, Davis BR, Geltman E, Hayes D, et al. Uniformity of captopril benefit in the SAVE study: Subgroup analysis. *Eur Heart J*. 1994;15(SUPPL. B):2-8.

Newman TJ, Maskin CS, Dennick LG, Meyer JH, Hallows BG, Cooper WH. Effects of captopril on survival in patients with heart failure. *Am J Med*. 1988;84(3A) p140-4.

Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996;334(21):1349-55.

Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344(22):1651-8.

Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. *Circulation*. 1996;94(11):2793-9.

Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327(10) p669-77.

Pflugfelder PW, Baird MG, Tonkon MJ, DiBianco R, Pitt B. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawal in chronic heart failure: a double-blind, placebo-controlled study of quinapril. The Quinapril Heart Failure Trial Investigators. *J Am Coll Cardiol*. 1993;22(6):1557-63.

Pitt B, Yusuf S, for the SOLVD Investigators. Studies of left ventricular dysfunction (SOLVD) subgroup results. *J Am Coll Cardiol*. 1992;19:215A.

Plehn JF, Krause-Steinrauf H, Anand IS, et al. Effect of race on cause-specific cardiovascular mortality in BEST. *Circulation*. 2000;102 (suppl 2)(18).

Pouleur HG, Konstam MA, Udelson JE, Rousseau MF. Changes in ventricular volume, wall thickness and wall stress during progression of left ventricular dysfunction. The SOLVD Investigators. *J Am Coll Cardiol*. 1993;22(4 Suppl A):43A-48A.

Sharpe DN, Murphy J, Coxon R, et al. Enalapril in patients with chronic heart failure: a placebo controlled randomized double-blind study. *Circulation*. 1984;70:271-8.

Swedberg K, Kjekshus J, Snapinn SOLVD Long-term survival in severe heart failure in patients treated with enalapril. Ten year follow-up of CONSENSUS I. *Eur Heart J*. 1999;20(2) p136-9.

The Beta-Blocker Evaluation of Survival Trial Investigators (BEST). A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344(22):1659-67.

The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy: the randomized evaluation of strategies for left ventricular dysfunction pilot study. *Circulation*. 2000;101(4) p378-84.

The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325(5):293-302.

Torp-Pedersen C, Kober L, Carlsen J. Angio-converting enzyme inhibition after myocardial infarction: the Trandolapril Cardiac Evaluation Study. *Am Heart J*. 1996;132(1 Pt 2 Su):235-43.

van Veldhuisen DJ, Genth-Zotz S, Brouwer J, Boomsma F, Netzer T, Man T, Veld AJ, et al. High-versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril. *J Am Coll Cardiol*. 1998;32(7) p1811-8.

Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet*. 1993;342(8885) p1441-6.

Wedel H, DeMets D, Deedwania P, et al. Challenges of subgroup analyses in multinational clinical trials: Experiences from the MERIT-HR trial. *Am Heart J*. 2001;142:502-11.

Widimsky J, Kremer HJ, Jerie P, Uhlir O. Czech and Slovak spirapril intervention study (CASSIS). A randomized, placebo and active-controlled, double-blind multicentre trial in patients with congestive heart failure. *European Journal of Clinical Pharmacology*. 1995;49(1-2) p95-102.

Wisenbaugh T, Katz I, Davis J, Essop R, Skoularigis J, Middlemost S, et al. Long-term (3-month) effects of a new beta-blocker (nebivolol) on cardiac performance in dilated cardiomyopathy. *J Am Coll Cardiol*. 1993;21(5):1094-100.

Witchitz S, Cohen-Solal A, Dartois N, Weisslinger N, Juste K, Darmon J Y. Treatment of heart failure with celiprolol, a cardioselective beta blocker with beta-2 agonist vasodilatory properties. The CELICARD Group. *Am J Cardio*. 2000;85(12) p1467-71.

Woodley SL, Gilbert EM, Anderson JL, O'Connell JB, Deitchman D, Yanowitz FG, et al. Beta-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. *Circulation*. 1991;84(6):2426-41.

Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Bristow MR, Cohn JN, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N Engl J Med*. 2001;344(18):1358-65.

Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Lukas MA, Young ST. Response of black heart failure patients to carvedilol [abstract]. *J Am Coll Cardiol*. 1997;29:284A.

Yusuf S, Nicklas JM, Timmis G, Breneman G, Jafri SM, Duvernoy WFC, et al. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med*. 1992;327(10):685-691.

Rejected Articles

Acanfora D, Lanzillo T, Papa A, Longobardi G, Furgi G, Rengo C, et al. Congestive heart failure in elderly patients: controlled study of delapril versus captopril. *Am J Cardiol*. 1995;75(18): 37F-43F.

Afzal A, Ananthasubramaniam K, Sharma N, al-Malki Q, Ali AS, Jacobsen G, et al. Racial differences in patients with heart failure. *Clin Cardiol*. 1999;22(12):791-4.

Afzal A, Brar JS, Ali AS, et al. Racial differences in patients with chest pain syndrome and abnormal coronary angiogram. *Chest*. 1997;112:245.

Ajayi AA, Balogun MO, Oyewo EA, Ladipo GO. Enalapril in African patients with congestive cardiac failure. *Br J Clin Pharmacol*. 1989;27(3) p400-3.

Akinkugbe OO, Nicholson GD, Cruickshank JK. Heart disease in blacks of Africa and the Caribbean. Saunders E. (editor). *Cardiovascular Disease in Blacks*. Philadelphia: F.A. Davis, 1991:377-91.

Alexander M, Grumbach K, Selby J, et al. Hospitalization for congestive heart failure: explaining racial differences. *JAMA*. 1990;263:2344-6.

Ambrosioni E, Borghi C, Magnani B. Survival of myocardial infarction long-term evaluation (SMILE) study: rationale, design, organization, and outcome definitions. *Control Clin Trials*. 1994;15(3):201-10.

Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med*. 1995;332(2):80-85.

American Heart Association. Heart and Stroke Facts: 1996 Statistical Supplement. Dallas, Texas: American Heart Association, 1996, 15.

Anderson F, Nilsson B, Gundersen T, Swedberg K, Amtorp O, Remes J. The effect on healthcare costs of adding ramipril to conventional therapy for patients with congestive heart failure. *Br J Med Econ*. 1995;8(3):125-135.

Anderson JL, Lutz JR, Gilbert EM, Sorensen SG, Yanowitz FG, Menlove RL, et al. A randomized trial of low-dose beta-blockade therapy for idiopathic dilated cardiomyopathy. *Am J Cardio*. 1985;55(4) p471-5.

Andersson B, Hamm C, Persson S, Wikstrom G, Sinagra G, Hjalmarson A, et al. Improved exercise hemodynamic status in dilated cardiomyopathy after beta-adrenergic blockade treatment. *J Am Coll Cardiol*. 1994;23(6):1397-404.

Arcensio SR, Barretto AC, Szambock F, Mady C, Arteaga E, da Luz PL, et al. [Comparative study between ibopamine and captopril in mild and moderate heart failure. A double-blind study]. *Arq Bras Cardiol*. 1994;63(5):409-13.

Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardio*. 1997;80(2) p207-9.

Aronow WS, Ahn C, Kronzon J. Congestive heart failure, coronary events and atherothrombotic brain infarction in elderly blacks and whites with systemic hypertension and with and without echocardiographic and eletrocardiographic evidence of left ventricular hypertrophy. *Am J Cardiol*. 1991;67:295-299.

Aronow WS, Greenfield RS, Alimadadian H, et al. Effect of the vasodilator trimazosin vs. placebo on exercise performance in chronic left ventricular failure. *Am J Cardiol*. 1977;40:789-793.

Aronow WS, Lurie M, Turbow M, et al. Effect of prazosin vs. placebo on chronic left ventricular heart failure. *Circulation*. 1979;59:344-350.

Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Australia/New Zealand Heart Failure Research Collaborative Group. *Lancet*. 1997;349(9049):375-80.

Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine—is this a cause for concern? *Arch Int Med.* 2000;160(N5):685-693.

Ball SG, Hall AS, Mackintosh AF, et al. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet.* 1993;342(8875) p821-8.

Bangdiwala SI, Weiner DH, Bourassa MG, Friesinger GC 2d, Ghali JK, Yusuf S. Studies of Left Ventricular Dysfunction (SOLVD) Registry: rationale, design, methods and description of baseline characteristics. *Am J Cardiol.* 1992;70(3):347-53.

Barabino A, Galbariggi G, Pizzorni C, et al. Comparative effects of long-term therapy with captopril and ibopamine in chronic congestive heart failure in old patients. *Cardiology*. 1991;78:289-296.

Barr CS, Lang CC, Hanson J, Arnott M, Kennedy N, Struthers AD. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. *Am J Cardio.* 1995;76(17):1259-1265.

Baruch L, Anand I, Cohen IS, Ziesche S, Judd D, Cohn JN. Augmented short- and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure. Vasodilator Heart Failure Trial (V-HeFT) Study Group. *Circulation.* 1999;99(20):2658-64.

Bayliss J, Canepa-Anson R, Norell M, Poole-Wilson P, Sutton G. The renal response to neuroendocrine inhibition in chronic heart failure: double-blind comparison of captopril and prazosin. *Eur Heart J.* 1986;7(10):877-84.

Beermann B, Nyquist O, Hoglund C, Jacobsson KA, Naslund U, Jensen-Urstad M. Acute haemodynamic effects and pharmacokinetics of ramipril in patients with heart failure. A placebo controlled three-dose study. *Eur J Clin Pharmacol.* 1993;45(3):241-6.

Behrens S, Ney G, Fisher SG, Fletcher RD, Franz MR, Singh SN. Effects of amiodarone on the circadian pattern of sudden cardiac death (Department of Veterans Affairs Congestive Heart Failure-Survival Trial of Antiarrhythmic Therapy). *Am J Cardiol.* 1997;80(1):45-8.

Benedict CR, Shelton B, Johnstone DE, Francis G, Greenberg B, Konstam M, et al. Prognostic significance of plasma norepinephrine in patients with asymptomatic left ventricular dysfunction. SOLVD Investigators. *Circulation.* 1996;94(4):690-7.

Beneficial effects of captopril on prognosis in patients with acute myocardial infarction. *Chinese Journal of Cardiology.* 1996;24(3):187-190.

Berger PB, Holmes DR Jr, Ohman EM, O'Hanesian MA, Murphy JG, Schwartz RS, et al. Restenosis, reocclusion and adverse cardiovascular events after successful balloon angioplasty of occluded versus nonoccluded coronary arteries. Results from the Multicenter American Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MARCATOR). *J Am Coll Cardiol.* 1996;27(1):1-7.

Bergler-Klein J, Sochor H, Pouleur H, Pacher R, Porenta G, Glogar D. Safety of concomitant potassium-sparing diuretics in angiotensin-converting enzyme inhibitor therapy in severe congestive heart failure. *J Cardiovasc Pharmacol.* 1994;24(2):194-198.

The BEST Steering Committee, Design of the Beta-Blocker Evaluation Survival Trial (BEST). *Am J Cardio*. 1995;75(17) p1220-3.

The Beta-Blocker Evaluation of Survival Trial Investigators (BEST). A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med.* 2001;344(22):1659-67.

Beynon JH, Pathy MS. An open, parallel group comparison of quinapril and captopril, when added to diuretic therapy, in the treatment of elderly patients with heart failure. *Curr Med Res Opin.* 1997;13(10) p583-92.

Boccanelli A, Zachara E, Liberatore SM, Carboni GP, Prati PL. Addition of captopril versus increasing diuretics in moderate but deteriorating heart failure: a double-blind comparative trial. *Postgrad Med J.* 1986;62 Suppl 1:184-7.

Bohler S, Saubadu S, Scheldewaert R, Figulla HR. Betaxolol versus carvedilol in chronic heart failure (BETACAR study). Rationale and design. *Arzneimittelforschung.* 1999;49(4):311-7.

Borghi C, Ambrosioni E, Magnani B. Effects of the early administration of zofenopril on onset and progression of congestive heart failure in patients with anterior wall acute myocardial infarction. The SMILE Study Investigators. Survival of Myocardial Infarction Long-term Evaluation. *Am J Cardiol.* 1996;78(3):317-22.

Borghi C, Bacchelli S, Esposti DD, Bignamini A, Magnani B, Ambrosioni E. Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension. SMILE Study Investigators. Survival of Myocardial Infarction Long-term Evaluation. *Am J Hypertens.* 1999;12(7):665-72.

Borghi C, Marino P, Zardini P, Magnani B, Collatina S, Ambrosioni E. Short- and long-term effects of early fosinopril administration in patients with acute anterior myocardial infarction undergoing intravenous thrombolysis: results from the Fosinopril in Acute Myocardial Infarction Study. FAMIS Working Party. *Am Heart J.* 1998;136(2):213-25.

Borghi C, Magelli C, Costa FV, Magnani B, Ambrosioni E. Captopril improves hemodynamic response to static exercise in patients with congestive heart failure: a double-blind, placebo-controlled, randomized trial. *Clin Cardiol.* 1990;13(5):329-34.

Bounhoure JP, Bottineau G, Lechat P, et al. Apport du perindopril au traitement de l'insuffisance cardiaque chronique congestive. *Arch Mal Coeur.* 1989;82:73-8.

Bourassa MG, Gurne O, Bangdiwala SI, Ghali JK, Young JB, Rousseau M, Johnstone DE, Yusuf S. Natural history and patterns of current practice in heart failure. The Studies of Left Ventricular Dysfunction (SOLVD) Investigators. *J Am Coll Cardiol.* 1993;22(4 Suppl A):14A-19A.

Braunwald E. Expanding indications for beta-blockers in heart failure. *N Engl J Med.* 2001;344(22):1711-12.

Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation.* 1996;94:2807-2816.

Bristow MR, O'Connell JB, Gilbert EM, French WJ, Leatherman G, Kantrowitz NE, et al. Dose-response of chronic beta-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. Bucindolol Investigators. *Circulation.* 1994;89(4) p1632-42.

Brown EJ Jr, Chew PH, MacLean A, Gelperin K, Ilgenfritz JP, Blumenthal M. Effects of fosinopril on exercise tolerance and clinical deterioration in patients with chronic congestive heart failure not taking digitalis. Fosinopril Heart Failure Study Group. *Am J Cardio.* 1995;75(8):596-600.

Buchwald A, Unterberg C, van der Does R, Wiegand V. [Acute hemodynamic effects of the vasodilator beta blocker carvedilol in heart failure]. *Z Kardiol.* 1990;79(6):424-8.

Bulpitt CJ, Fletcher AE, Dossegger L, Neiss A, Nielsen T, Viergutz S. Quality of life in chronic heart failure: cilazapril and captopril versus placebo. Cilazapril-Captopril Multicentre Group. *Heart.* 1998;79(6):593-8.

Bussmann WD, Storger H, Hadler D, et al. Long-term treatment of severe chronic heart failure with captopril: a double-blind randomized, placebo-controlled long-term study. *J Cardiovasc Pharmacol.* 1987;9(suppl. 2):S50-S60.

Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). *Am Heart J.* 1997;134(1):44-54.

Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. The Captopril-Digoxin Multicenter Research Group. *JAMA.* 1988;259(4):539-44.

Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol.* 1983;63:755-763.

Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. *J Card Fail.* 1999;5(3):178-87.

Chalmers JP, West MJ, Cyran J, De La Torre D, Englert M, Kramar M, et al. Placebo-controlled study of lisinopril in congestive heart failure: a multicentre study. *J Cardiovasc Pharmacol.* 1987;9 Suppl 3 pS89-97.

Chantrel F, Moulin B, Hannedouche T. Blood pressure, diabetes and diabetic nephropathy. *Diabetes Metab.* 2000;26 Suppl 4:37-44.

Chizzola PR, Freitas HF, Caldas MA, da Costa JM, Meneghetti C, Marinho NV, et al. Effects of carvedilol in heart failure due to dilated cardiomyopathy. Results of a double-blind randomized placebo-controlled study (CARIBE study). *Arquivos Brasileiros De Cardiologia.* 2000;74(3) p233-42.

Chrysant SG, Gollub S, Dunn MI, et al. Hemodynamic and metabolic effects of enalapril in patients with heart failure. *Clin Cardiol.* 1985;8:585-590.

CIBIS Investigators and Committees, A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation.* 1994;90(4) p1765-73.

CIBIS II Investigators and Committee, The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353(9146):9-13.

The CIBIS II Scientific Committee. Design of the cardiac insufficiency bisoprolol study II (CIBIS II). *Fund Clin Pharmacol.* 1997;11:38-42.

Cice G, Tagliamonte E, Ferrara L, Iacono A. Efficacy of carvedilol on complex ventricular arrhythmias in dilated cardiomyopathy: double-blind, randomized, placebo-controlled study. *Eur Heart J.* 2000;21(15):1259-64.

Circo A, Platania F, Mangiameli S, Putignano E. Multicenter, randomized, placebo-controlled, double-blind study of the safety and efficacy of oral delapril in patients with congestive heart failure. *Am J Cardiol.* 1995;75(18):18F-24F.

Cleland JG, Armstrong P, Horowitz JD, Massie B, Packer M, Poole-Wilson PA, et al. Baseline clinical characteristics of patients recruited into the assessment of treatment with lisinopril and survival study. *Eur J Heart Fail.* 1999;1(1):73-9.

Cleland JG, Dargie HJ, Gillen G, Robertson I, East BW, Ball SG, et al. Captopril in heart failure: a double-blind study of the effects on renal function. *J Cardiovasc Pharmacol.* 1986;8(4):700-6.

Cleland JG, Erhardt L, Murray G, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators. *Eur Heart J.* 1997;18(1):41-51.

Cleland JG, Pennel D, Ray S, Murray G, MacFarlane P, Cowley A, et al. The carvedilol hibernation reversible ischaemia trial; marker of success (CHRISTMAS). The CHRISTMAS Study Steering Committee and Investigators. *Eur J Heart Fail.* 1999;1(2):191-6.

Cleland JG, Tendera M, Adamus J, Freemantle N, Gray CS, Lye M, et al. Perindopril for elderly people with chronic heart failure: the PEP-CHF study. The PEP investigators. *Eur J Heart Fail.* 1999;1(3) p211-7.

Cleland JGF, Dargie HJ, Hodsman GP, et al. Captopril in heart failure: a double blind controlled trial. *Br Heart J.* 1984;52:530-5.

Cleland JGF, Dargie HJ, Ball SG, et al. Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. Br Heart J. 1985;54:305-311.

Cleland JGF, Shah D, Krikler S, Frost G, Oakley CM. Angiotensin-converting enzyme-inhibitors, left-ventricular dysfunction, and early heart-failure. *Am J Cardio.* 1992;70(N10. OCT 8):C55-C61.

Clement DL, De Buyzere M, Tomas M, Vanavermaete G. Long-term effects of clinical outcome with low and high dose in the Captopril in Heart Insufficient Patients Study (CHIPS). *Acta Cardiol*. 2000;55(1):1-7.

Cohn JN, Archibald DG, Ziesche S, et al. Effects of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med*. 1986;314:1547-1552.

Cohn JN, Fowler MB, Bristow MR, Colucci WS, Gilbert EM, Kinhal V, et al. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. *Journal of Cardiac Failure*. 1997;3(3) p173-9.

Cohn JN, Goldstein SO, Greenberg BH, Lorell BH, Bourge RC, Jaski BE, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. *N Engl J Med*. 1998;339(25):1810-6.

Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991;325:303-10.

Cohn JN, Tognoni G, Glazer RD, Spormann D, Hester A. Rationale and design of the Valsartan Heart Failure Trial: a large multinational trial to assess the effects of valsartan, an angiotensin-receptor blocker, on morbidity and mortality in chronic congestive heart failure. *J Card Fail*. 1999;5(2):155-60.

Colfer HT, Ribner HS, Gradman A, Hughes CV, Kapoor A, Laidlaw JC. Effects of once-daily benazepril therapy on exercise tolerance and manifestations of chronic congestive heart failure. The Benazepril Heart Failure Study Group. *Am J Cardio*. 1992;70(3) p354-8.

Colfer HT, Ribner HS, Gradman A, et al. Effects of once-daily benazepril therapy on exercise tolerance and manifestations of chronic congestive heart failure. *Am J Cardiol*. 1992;70:354-358.

Colucci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation*. 1996;94:280-2806.

Colucci WS, Sonnenblick EH, Adams KF, Berk M, Brozena SC, Cowley AJ, et al. Efficacy of phosphodiesterase inhibition with milrinone in combination with converting enzyme inhibitors in patients with heart failure. The Milrinone Multicenter Trials Investigators. *J Am Coll Cardiol*. 1993;22(4 Suppl A):113A-118A.

Colucci WS, Wynne J, Holman BL, et al. Long-term therapy of heart failure with prazosin: a randomized double blind trial. *Am J Cardiol*. 1980;45:337-344.

Comstock GW. An epidemiological study of blood pressure levels in a biracial community in the southern United States. *Am J Hygiene.* 1957;65:271-315.

Conradson TB. Hydralazine vs. placebo in CHF-preliminary results from a multicenter long-term study in Sweden. *Acta Med Scand*. 1981;652(suppl):177-180.

Copie X, Pousset F, Lechat P, Jaillon P, Guize L, Le Heuzey JY. Effects of beta-blockade with bisoprolol on heart rate variability in advanced heart failure: analysis of scatterplots of R-R intervals at selected heart rates. *Am Heart J*. 1996;132(2 Pt 1):369-75.

Coughlin SS, Myers L, Michaels RK. What explains black-white differences in survival in idiopathic dilated cardiomyopathy? The Washington, DC, dilated cardiomyopathy study. *Journal of the National Medical Association*. 1997;89(N4):277-282.

Council on Ethical and Judicial Affairs. Black-white disparities in health. *JAMA*. 1990;263:2344-6.

Cowley AJ, Stainer K, Wynne RD, Rowley JM, Hampton JR. Comparison of the effects of captopril and enoximone in patients with severe heart failure: a placebo controlled double-blind study. *Int J Cardiol*. 1989;24(3):311-6.

Creager MA, Massie BM, Fascon DP, et al. Acute and long-term effects of Enalapril on the cardiovascular response to exercise and exercise tolerance in patients with congestive heart failure. JACC. 1985;6:163-70.

Cucchini F, Compostella L, Papalia D, de Domenico R, Iavernaro A, ZeppelliniR. [Chronic treatment of dilated cardiomyopathy by beta blocking agents. Clinical and hemodynamic follow-up]: <Original> Trattamento cronico della cardiomiopatia dilatativa con betabloccanti. Controllo clinico ed emodinamico a distanza. *Giornale Italiano Di Cardiologia*. 1988;18(10) p835-42.

Currie PJ, Kelly MJ, McKenzie A, Harper RW, Lim YL, Federman J, et al. Oral beta-adrenergic blockade with metoprolol in chronic severe dilated cardiomyopathy. *J Am Coll Cardiol*. 1984;3(1):203-9.

Davies RF, Beanlands DS, Nadeau C, Phaneuf D, Morris A, Arnold JM, et al. Enalapril versus digoxin in patients with congestive heart failure: a multicenter study. Canadian Enalapril Versus Digoxin Study Group. *J Am Coll Cardiol*. 1991;18(7):1602-9.

Debock VD, Mets T, Romagnoli M, Derde MP. Captopril treatment of chronic heart-failure in the very old. *Journals of Gerontology*. 1994;49(N3. MAY):M148-M152.

Denis B, Machecourt J. Renitec et insuffisance cardiaque. *Tempo Medical*. 1985;5:40-3.

Dickstein K, Aarsland T. Effect on exercise performance of enalapril therapy initiated early after myocardial infarction. Nordic Enalapril exercise Trial. *J Am Coll Cardiol*. 1993;22(4):975-83.

Dickstein K, Barvik S, Aarsland T. Effect of long-term enalapril therapy on cardiopulmonary exercise performance in men with mild heart failure and previous myocardial infarction. *J Am Coll Cardiol*. 1991;18:596-602.

Diercks GF, Janssen WM, van Boven AJ, Bak AA, de Jong PE, Crijns HJ, et al. Rationale, design, and baseline characteristics of a trial of prevention of cardiovascular and renal disease with fosinopril and pravastatin in nonhypertensive, nonhypercholesterolemic subjects with microalbuminuria (the Prevention of REnal and Vascular ENdstage Disease Intervention Trial PREVEND IT). *Am J Cardiol*. 2000;86(6):635-8.

Dorszewski A, Gohmann E, Dorszewski B, Werner GS, Kreuzer H, Figulla HR. Vasodilation by urapidil in the treatment of chronic congestive heart failure in addition to angiotensin-converting enzyme inhibitors is not beneficial: results of a placebo-controlled, double-blind study. *Journal of Cardiac Failure*. 1997;3(2) p91-6.

Dossegger L, Bernink, Braun, Burger, Calvert, Deimann, et al. Comparison of the effects of cilazapril and captopril versus placebo on exercise testing in chronic heart-failure patients—a double-blind, randomized, multicenter trial. *Cardiology*. 1995;86(S1):34-40.

Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. *J Am Coll Cardiol*. 1997;29(5):1060-6.

Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Effects of carvedilol on left ventricular regional wall motion in patients with heart failure caused by ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. *J Card Fail*. 2000;6(1):11-8.

Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). *Lancet*. 1994;344(8921):493-8.

Drexler H, Banhardt U, Meinertz T, Wollschlager H, Lehmann M, Just H. Contrasting peripheral short-term and long-term effects of converting enzyme inhibition in patients with congestive heart failure. A double-blind, placebo-controlled trial. *Circulation*. 1989;79(3) p491-502.

Dries DL, Exner DV, Gersh J, Cooper HA, Carson PE, Domanski MJ. Racial differences in the outcome of left ventricular dysfunction [published erratum appears in *N Engl J Med* 1999 Jul 22;341(4):298]. *N Engl J Med*. 1999;340(8):609-16.

Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2000;35(3) p681-9.

East MA, Peterson ED, Shaw LK, et al. Racial differences in the outcome of patients with diastolic heart failure: Results from the Duke Databank of Cardiovascular Disease. *Circulation.* 2000;102 (suppl)(18).

Eichhorn EJ, Domanski MJ, Adams K, et al. Effect of beta-blockade on mortality in African-Americans: The beta-blocker evaluation of survival trial. *Circulation.* 2000;102 (suppl 2)(18).

Eichhorn EJ, Domanski MJ, Bristow MR, et al. Hemodynamic, myocardial functional and neurohormonal responses to beta-blockade in Black vs. Non-Black patients in BEST. *Circulation.* 2000;102 (suppl II)(18).

Eichhorn EJ, Heesch CM, Barnett JH, Alvarez LG, Fass SM, Grayburn PA, et al. Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol.* 1994;24(5):1310-20.

Enalapril CHF Investigators. Long-term effects of enalapril in patients with congestive heart failure: a multicenter, placebo-controlled trial. *Heart Failure.* 1987;3:102-107.

Engelmeier RS, O'Connell JB, Walsh R, Rad N, Scanlon PJ, Gunnar RM. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial. *Circulation.* 1985;72(3) p536-46.

Erdmann E, Lechat P, Verkenne P, Wiemann H. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *Euro J Heart Failure.* 2001;3:469-479.

Eriksson SV, Offstad J, Kjekshus J. M-mode echocardiography in patients with severe congestive heart failure. A subgroup analysis in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *Drugs.* 1990;39 Suppl 4:43-8; discussion 53-4.

Erlemeier HH, Kupper W, Bleifeld W. Comparison of hormonal and haemodynamic changes after long-term oral therapy with pimobendan or enalapril--a double-blind randomized study. *Eur Heart J.* 1991;12(8):889-99.

Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patiens with left ventricular dysfunction. *N Eng J Med.* 2001;344(18):1351-7.

Exner DV, Dries DL, Domanski MJ, et al. Enalapril therapy and outcome in Black versus White patients enrolled in the studies of left ventricular dysfunction. *Circulation.* 2000;102(18).

Fagan TC. Diltiazem: its place in the antihypertensive armamentarium. *J Cardiovasc Pharmacol.* 1991;18 Suppl 9:S26-31.

Fagerberg B. Screening, endpoint classification, and safety monitoring in the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Eur J Heart Fail.* 2000;2(3):315-24.

Fang J, Madhavan S, Alderman MH. The association between birthplace and mortality from cardiovascular causes among black and white residents of New York City. *N Engl J Med.* 1996;335:1545-51.

Figulla HR, Luig H, Nieschlag F, Kreuzer H. [Clinical and hemodynamic effects of nisoldipine and captopril in heart failure: a double-blind comparative study of long and short-term effects]. *Z Kardiol.* 1987;76(3):167-74.

Fisher ML, Gottlieb SS, Plotnick GD, Greenberg NL, Patten RD, Bennett SK, et al. Beneficial effects of metoprolol in heart failure associated with coronary artery disease: a randomized trial. *J Am Coll Cardiol.* 1994;23(4) p943-50.

Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet.* 2000;355(9215) p1575-81.

Fletcher AE, Bulpitt CJ, Chase DM, Collins WC, Furberg CD, Goggin TK, et al. Quality of life with three antihypertensive treatments. Cilazapril, atenolol, nifedipine. *Hypertension.* 1992;19(6 Pt 1):499-507.

Forman DE, Chander RB, Lapane KL, Shah P, Stoukides J. Evaluating the use of angiotensin-converting enzyme inhibitors for older nursing home residents with chronic heart failure. *JAGS.* 1998;46(12) p1550-4.

Franciosa JA, Cohn JN. Sustained hemodynamic effects without tolerance during lon-term isosorbide dinitrate treatment of chronic left ventricular failure. *Am J Cardiol*. 1980;45:648-654.

Franciosa JA, Jordan RA, Wilen MM, et al. Minoxidil in patients with chronic left heart failure: contrasting hemodynamic and clinical effects in a controlled trial. *Circulation*. 1984;70:63-68.

Franciosa JA, Nordstrom LA Cohn JN. Nitrate therapy for congestive heart failure. *JAMA*. 1978;240:443-446.

Franciosa JA, Weber KT, Levine TB, et al. Hydralazine in the long-term treatment of chronic heart failure: lack of difference from placebo. *Am Heart J*. 1982;104:587-594.

Franciosa JA, Wilen MM, Jordan RA. Effects of enalapril, a new angiotensin-converting enzyme inhibitor, in a controlled trial in heart failure. *J Am Coll Cardiol*. 1985;5(1) p101-7.

Francis CK. Report of the NHLBI working group on research in coronary heart disease in blacks: Issues and challenges. *J Nat Med Assoc.* 1995;87(suppl):597-603.

Francis CK. Heart failure in elderly African-Americans. *Am J Geriatr Cardiol.* 1997;6(5):50-68.

Fuchs W. Comparison of the safety and efficacy of delapril with captopril in outpatients with congestive heart failure. *Am J Cardiol.* 1995;75(18):29F-36F.

Funck-Brentano C, Lancar R, Le Heuzey JY, Lardoux H, Soubrie C, Lechat P. Predictors of medical events in patients enrolled in the cardiac insufficiency bisoprolol study (CIBIS): a study of the interactions between beta-blocker therapy and occurrence of critical events using analysis of competitive risks. *Am Heart J.* 2000;139(2 Pt 1) p262-71.

Gallagher EJ, Viscoli CM, Horwitz RiI The relationship of treatment adherence to the risk of death after myocardial-infarction in women. *JAMA.* 1993;270(N6):742-744.

Gambassi G, Forman DE, Lapane KL, Mor V, Sgadari A, Lipsitz LA, et al. Management of heart failure among very old persons living in long-term care: has the voice of trials spread? The SAGE Study Group. *Am Heart J.* 2000;139(1 Pt 1) p85-93.

Gambassi G, Lapane KL, Sgadari A, Carbonin P, Gatsonis C, Lipsitz LA, et al. Effects of angiotensin-converting enzyme inhibitors and digoxin on health outcomes of very old patients with heart failure. SAGE Study Group. Systematic Assessment of Geriatric drug use via Epidemiology. *Arch Intern Med*. 2000;160(1) p53-60.

Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA.* 1995;273(18):1450-1456.

Gattis WA, Hasselblad V, Whellan DJ, O'Connor CM. Reduction in heart failure events by the addition of a clinical pharmacist to the heart failure management team: results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study. *Arch Intern Med.* 1999;159(16):1939-45.

Gattis WA, Larsen RL, Hasselblad V, Bart BA, O'Connor CM. Is optimal angiotensin-converting enzyme inhibitor dosing neglected in elderly patients with heart failure? *Am Heart J.* 1998;136(1) p43-8.

Gavazzi A, Marioni R, Campana C, Montemartini C. Comparative trial of quinapril versus captopril in mild to moderate congestive heart failure. Quinapril/Captopril Congestive Heart Failure Study Group. *J Hypertens Suppl.* 1994;12(4):S89-93.

Genth-Zotz S, Zotz RJ, Sigmund M, Hanrath P, Hartmann D, Bohm M, et al. MIC trial: metoprolol in patients with mild to moderate heart failure: effects on ventricular function and cardiopulmonary exercise testing. *Eur J Heart Fail.* 2000;2(2) p175-81.

Geronimus AT, Bound J, Waidmann TA, et al. Excess mortality among blacks and whites in the United States. *N Engl J Med.* 1996;335:1552-8.

Gerstein HC, Yusuf S, Mann JFE, Hoogwerf B, Zinman B, Held C, et al. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the hope study and micro-hope substudy. *Lancet*. 2000;355(N9200. JAN 22):253-259.

Ghali JK, Kadakia S, Cooper R, et al. Precpitating factors leading to decompensation of heart failure: traits among urban blacks. *Arch Intern Med*. 1988;148:2013-6.

Ghali JK, Pina IL, Gottlieb SS, et al. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). *Circulation*. 2002;105(13):1585-91.

Gheorghiade M, Benatar D, Konstam MA, Stoukides CA, Bonow RO. Pharmacotherapy for systolic dysfunction: a review of randomized clinical trials. *Am J Cardio*. 1997;80(N8B,SI):H14-H27.

Ghose JC, Chakraborty S, Mondal M, Bhandari B. Effect of vasodilator therapy on mortality in chronic congestive heart failure. *Journal of the Association of Physicians of India*. 1993;41(5) p269-71.

Gilbert EM, Anderson JL, Deitchman D, Yanowitz FG, O'Connell JB, Renlund DG, et al. Long-term beta-blocker vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: a double-blind, randomized study of bucindolol versus placebo. *Am J Med*. 1990;88(3) p223-9.

Giles TD, for Lisinopril Chronic Heart Failure Group. Lisinopril treatment of congestive heart failure-results of a placebo controlled trial. *Circulation*. 1990;82(suppl 4):III-323.

Giles TD, Katz R, Sullivan JM, Wolfson P, Haugland M, Kirlin P, et al. Short- and long-acting angiotensin-converting enzyme inhibitors: a randomized trial of lisinopril versus captopril in the treatment of congestive heart failure. The Multicenter Lisinopril-Captopril Congestive Heart Failure Study Group. *J Am Coll Cardiol*. 1989;13(6):1240-7.

Gilligan DM, Chan WL, Joshi J, Clarke P, Fletcher A, Krikler S, et al. A double-blind, placebo-controlled crossover trial of nadolol and verapamil in mild and moderately symptomatic hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1993;21(7):1672-9.

Gillum RF. The epidemiology of cardiovascular disease in black Americans [editorial; comment] *N Engl J Med*. 1996;335(21):1597-9.

Gillum RF. Coronary heart disease in black populations. I. Mortality and morbidity. *Am Heart J*. 1982;104:839-51.

Gillum RF. Epidemiology of hypertension in African American women. *Am Heart J*. 1986;131:385-95.

Gillum RF. Stroke in blacks. *Stroke*. 1988;19:1-9.

Gillum RF. Sudden coronary death in the United States. *Circulation*. 1989;79:756-65.

Gillum RF. Cardiovascular disease in the United States: an epidemiologic overview. Saunders E. (editor): *Cardiovascular Diseases in Blacks*. Philadelphia: F.A. Davis, 1991;3-16.

Gillum RF. Epidemiology of heart failure in the United States. *Am Heart J*. 1993;126:1042-1047.

Gillum RF. Trends in acute myocardial infarction and coronary heart disease death in the United States. *J Am Coll Cardiol*. 1994;23:1273-7.

Gillum RF, Ingram DI. The relation between residence in the Southeast region of the United States and stroke incidence and death: the NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol*. 1996;144:665-73.

Goldstein S, Hjalmarson A. The mortality effect of metoprolol CR/XL in patients with heart failure: results of the MERIT-HF Trial. *Clinical Cardiology*. 1999;22 Suppl 5 pV30-5.

Gordon M. Evaluation of the Efficacy and Safety of Ramipril (HOE 498) in Patients with Congestive Heart Failure in a Placebo-controlled Trial.(unpublished report) 1991.

Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockers on mortality among high risk and low risk patients after myocardial infarction. *N Engl J Med*. 1998;339:489-97.

Gretler DD, Fumo MT, Nelson KS, et al. Ethnic differences in circadian hemodynamic profile. *Am J Hypertens*. 1994;7:7-14.

Gundersen T, Wiklund I, Swedberg K, Amtorp O, Remes J, Nilsson B. Effects of 12 weeks of ramipril treatment on the quality of life in patients with moderate congestive heart failure: results of a placebo-controlled trial. Ramipril Study Group. *Cardiovascular Drugs and Therapy.* 1995;9(4) p589-94.

Gustafsson I, Torppedersen C, Kober L, Gustafsson F, Hildebrandt P. Effect of the angiotensin-converting enzyme inhibitor trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after acute myocardial infarction. *J Am Coll Cardiol.* 1999;34(N1. JUL):83-89.

Habte B. The efficacy of hydrochlorothiazide, timolol and enalapril in Ethiopians with essential hypertension. *Ethiop Med J.* 1992;30(3):163-7.

Hager WD, Davis BR, Riba A, Moye LA, Wun CC, Rouleau JL, et al. Absence of a deleterious effect of calcium channel blockers in patients with left ventricular dysfunction after myocardial infarction: The SAVE Study Experience. SAVE Investigators. Survival and Ventricular Enlargement. *Am Heart J.* 1998;135(3):406-13.

Hahn B, Strauer BE. The influence of beta-adrenoceptor blockade on left ventricular function. *Br J Clin Pharmacol.* 1982;13(Suppl 2):305S-307S.

Haiat R, Piot O, Gallois H, Hanania G. Blood pressure response to the first 36 hours of heart failure therapy with perindopril versus captopril. French General Hospitals National College of Cardiologists. *J Cardiovasc Pharmacol.* 1999;33(6):953-9.

Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Acute Infarction Ramipril Efficacy. *Lancet.* 1997;349(9064):1493-7.

Hall AS, Winter C, Bogle SM, et al. The Acute Infarction Ramipril Efficacy (AIRE) Study: rationale, design, organization, and outcome definitions. *J Cardiovasc Pharmacol.* 1991;18(Suppl 2):S105-S109.

Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *J Am Coll Cardiol.* 1995;25(5):1154-61.

Hall WD, Kusek JW, Kirk KA, Appel LJ, Schulman G, Agodoa LY, et al. Short-term effects of blood pressure control and antihypertensive drug regimen on glomerular filtration rate: the African-American study of kidney disease and hypertension pilot study. *American Journal of Kidney Diseases.* 1997;29(N5):720-728.

Hammond IW, Alderman MH, Devereux RB. Contrast in cardiac anatomy and function between black and white patients with hypertension. *J Natl Med Assoc.* 1984;76:247-255.

Hampton JR. Choosing the right beta-blocker. A guide to selection. *Drugs.* 1994;48(4):549-68.

Han YL, Tong M, Jing Qm, Hu XL, Liu JQ. Combined therapy of captopril and spironolactone for refractory congestive-heart-failure. *Chinese Medical Journal.* 1994;107(N9. SEP):688-692.

Hansen JF, Hagerup L, Sigurd B, Pedersen F, Mellemgaard K, Pedersen-Bjergaard O, et al. Cardiac event rates after acute myocardial infarction in patients treated with verapamil and trandolapril versus trandolapril alone. Danish Verapamil Infarction Trial (DAVIT) Study Group. *Am J Cardiol.* 1997;79(6):738-41.

Harper RW, Calzton H, Middlebrook K, et al. The acute and chronic haemodynamic effects of prazosin in severe congestive heart failure. *Med J Aust.* 1980;2(suppl):36-38.

Hasford J, Bussmann WD, Delius W, Kopcke W, Lehmann K, Weber E. Design and analysis of the HYPREN-trial: safety of enalapril and prazosin in the initial treatment phase of patients with congestive heart failure. *Z Kardiol.* 1991;80 Suppl 2:21-7.

Havranek EP, Abrams F, Stevens E, Parker K. Determinants of mortality in elderly patients with heart failure: the role of angiotensin-converting enzyme inhibitors. *Arch Intern Med.* 1998;158(18):2024-8.

Haywood IJ. Coronary heart disease mortality/morbidity and risk in blacks. I. Clinical manifestations and diagnostic criteria: the experience with the Beta Blocker Heart Attack Trial. *Am Heart J*. 1984;108:787-93.

He J, Whelton PK. Epidemiology and prevention of hypertension. *Med Clin North Am.* 1997;81(5): 1077-97.

Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol*. 1997;30:27-34.

Herholz H, Goff DC, Ramsey DJ, Chan FA, Ortiz C, Labarthe DR, et al. Women and Mexican Americans receive fewer cardiovascular drugs following myocardial infarction than men and non-Hispanic whites: the Corpus Christi Heart Project, 1988-1990. *J Clin Epidemiol*. 1996; 49(3):279-87.

Herlitz J. Comparison of lisinopril versus digoxin for congestive heart failure during maintenance diuretic therapy. The Lisinopril-Digoxin Study Group. *Am J Cardiol*. 1992;70(10):84C-90C.

Herlitz J, Waagstein F, Lindqvist J, Swedberg K, Hjalmarson A. Effect of metoprolol on the prognosis for patients with suspected acute myocardial infarction and indirect signs of congestive heart failure (a subgroup analysis of the Goteborg Metoprolol Trial). *Am J Cardio*. 1997;80(9B) p40J-44J.

Herrlin B, Nyquist O, Sylven C. Induction of a reduction in haemoglobin concentration by enalapril in stable, moderate heart failure: a double blind study. *Br Heart J.* 1991;66(3):199-205.

Herrlin B, Sylven C, Nyquist O, Edhag O. Short term haemodynamic effects of converting enzyme inhibition before and after eating in patients with moderate heart failure caused by dilated cardiomyopathy: a double blind study. *Br Heart J*. 1990;63(1):26-31.

Higginbotham MB, Morris KG, Bramlet DA, et al. Long-term ambulatory therapy with prazosin vs. placebo for chronic heart failure: relation between clinical response and left ventricular function at rest and during exercise. *Am J Cardiol*. 1983;52:782-788.

Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA*. 2000;283(10);1295-302.

Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, KjekshusJ, et al. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169):2001-2007.

Hobbs RE. Results of the ATLAS study. High or low doses of ACE inhibitors for heart failure? *Cleve Clin J Med*. 1998;65(10):539-42.

Hood WB Jr, Youngblood M, Ghali JK, Reid M, Rogers WJ, Howe D, et al. Initial blood pressure response to enalapril in hospitalized patients (Studies of Left Ventricular Dysfunction [SOLVD]). *Am J Cardiol*. 1991;68(15):1465-8.

The HOPE study investigators. The HOPE (Heart Outcomes Prevention Evaluation) Study: the design of a large, simple randomized trial of an angiotensin-converting enzyme inhibitor (ramipril) and vitamin E in patients at high risk of cardiovascular events. *Can J Cardiol*. 1996;12(2):127-37.

Houghton AR, Harrison M, Cowley AJ. Haemodynamic, neurohumoral and exercise effects of losartan vs. captopril in chronic heart failure: results of an ELITE trial substudy. Evaluation of Losartan in the Elderly. *Eur J Heart Fail*. 1999;1(4):385-93.

Hughes CV, Wong M, Johnson G, Cohn JN. Influence of age on mechanisms and prognosis of heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation*. 1993;87(6 Suppl):VI111-7.

Hypertension detection and follow-up program cooperative group. Race, education, and prevalence of hypertension. *Am J Epidemiol*. 1977;106:351-361.

The International Steering Committee. Rationale, design, and organization of the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF). *Am J Cardio*. 1997;80(9B) p54J-58J.

Jansen RW, Gurwitz JH. Controversies surrounding the use of beta-blockers in older patients with cardiovascular-disease. *Drugs & Aging*. 1994;4(N3):175-183.

Jerie P, Kremer HJ, Uhlir O, Widimsky J. [A Czech and Slovak interventional study of spirapril (the CASSIS study). A randomized, double-blind, multicenter, placebo-controlled study in chronic heart failure]: <Original> Ceska a slovenska intervencni studie se spiraprilem (studie CASSIS). Randomizovana, dvojiteslepa, multicentricka studie, kontrolovana aktivne i placebem chronickeho srdecniho selhani. Za resitele studie CASSIS. *Vnitrni Lekarstvi*. 1997;43(6);351-8.

Johnstone D, Limacher M, Rousseau M, Liang CS, Ekelund L, Herman M, et al. Clinical characteristics of patients in studies of left ventricular dysfunction (SOLVD). *Am J Cardiol*. 1992;70(9):894-900.

Joy M, Hubner PJ, Thomas RD, et al. Long term use of enalapril in the treatment of patients with congestive heart failure. *Int J Cardiol*. 1987;16:137-44.

Just H, Drexler H, Taylor SH, Siegrist J, Schulgen G, Schumacher M. Captopril versus digoxin in patients with coronary artery disease and mild heart failure. A prospective, double-blind, placebo-controlled multicenter study. The CADS Study Group. *Herz*. 1993;18 Suppl 1 p436-43.

Kennedy HL, Brooks MM, Barker AH, Bergstrand R, Huther ML, Beanlands DS, et al. Beta-blocker therapy in the Cardiac Arrhythmia Suppression Trial. CAST Investigators. *Am J Cardiol*. 1994;74(7):674-80.

Keren G, Pardes A, Eschar Y, Koifman B, Scherez J, Geleranter I, et al. One-year clinical and echocardiographic follow-up of patients with congestive cardiomyopathy treated with captopril compared to placebo. *Israel Journal of Medical Sciences*. 1994;30(1);90-8.

Kjekshus J, Swedberg K. Enalapril for congestive heart failure. *Am J Cardio*. 1989;63(8);26D-32D.

Kleber FX, Laube A, Osterkorn K, et al. Captopril in mild to moderate heart failure after 18 months: effects on morbidity and mortality. *JACC*. 1987;9:42A (Abstr).

Kleber FX, Niemoller L, Doering W. Impact of converting enzyme inhibition on progression of chronic heart failure: results of the Munich Mild Heart Failure Trial. *British Heart Journal*. 1992;67(4):289-96.

Kleber FX, Reindl I, Wenzel M, Rodewyk P, Beil S, Kosloswki B, et al. Experiences with ACE inhibitors early after acute myocardial infarction. Rationale and design of the German Multicenter Study on the Effects of Captopril on Cardiopulmonary Exercise parameters post myocardial infarction (ECCE). *Herz*. 1993;18 Suppl 1:424-9.

Kleber FX, Sabin GV, Winter UJ, Reindl I, Beil S, Wenzel M, et al. Angiotensin-converting enzyme inhibitors in preventing remodeling and development of heart failure after acute myocardial infarction: results of the German multicenter study of the effects of captopril on cardiopulmonary exercise parameters (ECCE). *Am J Cardiol*. 1997;80(3A):162A-167A.

Knight EL, Glynn RJ, McIntyre KM, Mogun H, Avorn J. Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: results from the studies of left ventricular dysfunction (SOLVD). *Am Heart J*. 1999;138(5 Pt 1);849-55.

Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med*. 1995;333(25);1670-6.

Kober L, Torp-Pedersen C, Ottesen M, Burchardt H, Korup E, Lyngborg K. Influence of age on the prognostic importance of left ventricular dysfunction and congestive heart failure on long-term survival after acute myocardial infarction. TRACE Study Group. *Am J Cardiol*. 1996;78(2):158-62.

Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. *Circulation*. 1992;86(2):431-8.

Konstam V, Salem D, Pouleur H, Kostis J, Gorkin L, Shumaker S, et al. Baseline quality of life as a predictor of mortality and hospitalization in 5,025 patients with congestive heart failure. SOLVD Investigations. Studies of Left Ventricular Dysfunction Investigators. *Am J Cardiol.* 1996;78(8):890-5.

Kostis JB, Shelton B, Gosselin G, Goulet C, Hood WB Jr, Kohn RM, et al. Adverse effects of enalapril in the Studies of Left Ventricular Dysfunction (SOLVD). SOLVD Investigators. *Am Heart J.* 1996;131(2):350-5.

Kostis JB, Shelton BJ, Yusuf S, Weiss MB, Capone RJ, Pepine CJ, et al. Tolerability of enalapril initiation by patients with left ventricular dysfunction: results of the medication challenge phase of the Studies of Left Ventricular Dysfunction. *Am Heart J.* 1994;128(2):358-64.

Krishnamoorthy V, Quintana H, Dali S, et al. Heart failure with preserved systolic function in African Americans: The role of diabetes mellitus and obesity. *Circulation.* 2000;102 (suppl 2)(18).

Krum H. Beta-blockers in heart failure. The new wave' of clinical trials. *Drugs.* 1999;58(2):203-10.

Krum H, Gu A, Wilshire-Clement M, Sackner-Bernstein J, Goldsmith R, Medina N, et al. Changes in plasma endothelin-1 levels reflect clinical response to beta-blockade in chronic heart failure. *Am Heart J.* 1996;131(2):337-41.

Krum H, Sackner-Bernstein JD, Goldsmith RL, Kukin ML, Schwartz B, Penn J, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation.* 1995;92(6):1499-506.

Krum H, Shusterman N, MacMahon S, Sharpe N. Efficacy and safety of carvedilol in patients with chronic heart failure receiving concomitant amiodarone therapy. Australia/New Zealand Heart Failure Research Collaborative Group. *J Card Fail.* 1998;4(4):281-8.

Krum H, Tonkin A, Trotter A, Burton R, Garrett J, Lane G, et al. Effects of carvedilol, a vasodilator-beta-blocker, in patients with congestive heart failure due to ischemic heart disease. *Circulation.* 1995;92(2):212-218.

Krumholz HM, Wang Y, Parent EM, Mockalis J, Petrillo M, Radford MJ. Quality of care for elderly patients hospitalized with heart failure. *Arch Intern Med.* 1997;157(19):2242-7.

Kukin ML, Mannino MM, Freudenberger RS, Kalman J, Buchholz-Varley C, Ocampo O. Hemodynamic comparison of twice daily metoprolol tartrate with once daily metoprolol succinate in congestive heart failure. *J Am Coll Cardiol.* 2000;35(1):45-50.

Kumanyika S. Improving our diet - still a long way to go. *N Engl J Med.* 1996;335:236-52.

Lang RM, Elkayam U, Yellen LG, Krauss D, McKelvie RS, Vaughan DE, et al. Comparative effects of losartan and enalapril on exercise capacity and clinical status in patients with heart failure. The Losartan Pilot Exercise Study Investigators. *J Am Coll Cardiol.* 1997;30(4):983-91.

Lanska DJ, Peterson PM. Effects of interstate migration on the geographic distribution of stroke mortality in the United States. *Stroke.* 1995;26:554-61.

Lechat P, Escolano S, Golmard JL, Lardoux H, Witchitz S, Henneman JA, et al. Prognostic value of bisoprolol-induced hemodynamic effects in heart failure during the Cardiac Insufficiency BIsoprolol Study (CIBIS). *Circulation.* 1997;96(7):2197-205.

Lechat P, Garnham J, Desche P, et al. Efficacy and acceptability of preindopril in mild to moderate chronic congestive heart failure. *Am Heart J.* 1993;126:798-826.

Lechat P, Packer M, Chalon S, et al. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized clinical trials. *Circulation.* 1998;98:1184-91.

Lee DK, Marantz PR, Devereux RB. Left ventricular hypertrophy in black and white hypertensives. Standard electrocardiographic criteria overestimate racial differences. *J Am Med Assoc.* 1992;267:3294-3299.

Leier CV, Huss P, Magorien RD, et al. Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for congestive heart failure. *Circulation*. 1983;67:817-822.

Lemarie JC. Multicenter Double-Blind Placebo-Controlled Study of the Efficacy and Safety of Ramipril Administered Orally for 24 Weeks in the Treatment of Stable Chronic Congestive Cardiac Failure. (unpublished report) 1992.

Lewis BS, Rabinowitz B, Schlesinger Z, Caspi A, Markiewicz W, Rosenfeld T, et al. Effect of isosorbide-5-mononitrate on exercise performance and clinical status in patients with congestive heart failure. Results of the Nitrates in Congestive Heart Failure (NICE) Study. *Cardiology*. 1999;91(1):1-7.

Lewis GR. Lisinopril versus placebo in older congestive heart failure patients. *Am J Med*. 1988;85(3B):48-54.

Liao Y, Cooper RS, McGee DL. The relative effects of left ventricular hypertrophy, coronary artery disease, and ventricular dysfunction on survival among black adults. *JAMA*. 1995;273:1592-1597.

Lichstein E, Hager WD, Gregory JJ, Fleiss JL, Rolnitzky LM, Bigger JT Jr. Relation between beta-adrenergic blocker use, various correlates of left ventricular function and the chance of developing congestive heart failure. The Multicenter Diltiazem Post-Infarction Research Group. *J Am Coll Cardiol*. 1990;16(6):1327-32.

Littler WA, Sheridan DJ. Placebo controlled trial of felodipine in patients with mild to moderate heart failure. UK Study Group. *Br Heart J*. 1995;73(5):428-33.

Livingston IL. Social status, stress, and health: black Americans at risk. Livingston IL (editor). *Handbook of Black American Health*. Westport, Conn: Greenwood Press, 1994:236-52.

Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] Trial). *Am J Cardio*. 1992; 70(4):479-87.

Lombardi WL, Litwin SE. Angiotensin-converting enzyme inhibitors: congestive heart failure and beyond. *Coron Artery Dis.* 1999;10(6):361-8.

Lubsen J, Chadha DR, Yotof YT, Swedberg K. Meta-analysis of morbidity and mortality in five exercise capacity trials evaluating ramipril in chronic congestive cardiac failure. *Am J Cardio*. 1996;77(14):1191-1196.

Luparini R L, Celli V, Piccirillo G, Guidi V, Cacciafestam, Marigliano V. Carvedilol in elderly patients with chronic heart failure, a 12 weeks randomized, placebo controlled open trial. *Archives of Gerontology and Geriatrics*. 1999;29:275-282.

Maass L. Double-Blind Comparative Trial with Ramipril and Placebo in Patients with Heart Failure (NYHA Class III-IV) Stabilized on Digitalis and Furosemides. (unpublished report) 1991.

Maass L. Efficacy and Safety of Ramipril (HOE 498) in Patients with Congestive Heart Failure in a Double Blind Placebo Controlled Trial. (unpublished report) 1991.

Maass L. Evaluation of the Effect of Ramipril (HOE 498) on Exercise Duration, Invasive Cardiac Haemodynamics Profiles, and Safety in Patients with Congestive Heart Failure. (unpublished report) 1991.

MacFadyen RJ, Lees KR, Reid JL. Differences in first dose response to angiotensin converting enzyme inhibition in congestive heart failure: a placebo controlled study. *Br Heart J.* 1991;66(3):206-11.

MacFadyen RJ, Lees KR, Reid JL. Double blind controlled study of low dose intravenous perindoprilat or enalaprilat infusion in elderly patients with heart failure. *Br Heart J.* 1993;69(4):293-7.

Maggioni AP, Anand I, Masson S, et al. Non-ischemic congestive heart failure without renin-angiotensin-aldosterone and adrenergic systems activation in South African Blacks in Val-HeFT. *Circulation*. 2000;102(18).

Magnani B. Converting enzyme inhibition and heart failure. *Am J Med*. 1988;84(3A):87-91.

Magnani B, Magelli C. Captopril in mild heart failure: preliminary observations of a long-term, double-blind, placebo-controlled multicentre trial. *Postgraduate Medical Journal*. 1986;62 (Suppl 1):153-8.

Magorien RD, Unverferth DV, Leier CV. Hydralazine therapy in chronic congestive heart failure. *Am J Med*. 1984;77:267-274.

Markham RV, Corbett JR, Gilmore A, et al. Efficacy of prazosin in the management of chronic congestive heart failure: a six-month randomized, double-blind, placebo-controlled study. *Am J Cardiol*. 1983;51:1346-1352.

Massie B, Bourassa M, DiBianco R, Hess M, Konstam M, Likoff M, et al. Long-term oral administration of amrinone for congestive heart failure: lack of efficacy in a multicenter controlled trial. *Circulation*. 1985;71(5):963-71.

Massie BM, Berk MR, Brozena SC, Elkayam U, Plehn JF, Kukin ML, et al. Can further benefit be achieved by adding flosequinan to patients with congestive heart failure who remain symptomatic on diuretic, digoxin, and an angiotensin converting enzyme inhibitor? Results of the flosequinan-ACE inhibitor trial (FACET). *Circulation*. 1993;88(2):492-501.

Massie BM, Cleland JG, Armstrong PW, Horowitz JD, Packer M, Poole-Wilson PA, et al. Regional differences in the characteristics and treatment of patients participating in an international heart failure trial. The Assessment of Treatment with Lisinopril and Survival (ATLAS) Trial Investigators [published erratum appears in J Card Fail 1998 Jun;4(2):153]. *J Card Fail*. 1998;4(1):3-8.

Mathew J, Davidson S, Narra L. Etiology and characteristics of congestive heart failure in blacks. *Am J Cardiol*. 1996;78:1447-1450.

Mayet J, Shahi M, Foale RA. Racial differences in cardiac structure and function in essential hypertension. *Br Med J*. 1994;308:1011-1014.

McGarry R. Randomized, Double-Blind, Multicenter Study Comparing Benazepril to Digoxin and to Placebo as Add On Therapy to Diuretic in Patients with CHF, NYHA Class II-III During a 12-Week Treatment Period, GHBA-194. (unpublished report) 1991.

McGrath BP, Arnolda L, Matthews PG, Jackson B, Jennings G, Kiat H, et al. Controlled trial of enalapril in congestive cardiac failure. *British Heart Journal*. 1985;54(4):405-14.

McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation*. 1999;100(10):1056-64.

McMurray JJ. Major beta blocker mortality trials in chronic heart failure: a critical review. *Heart*. 1999;82 (Suppl 4):IV14-22.

Meade TW, Brosovic M, Chakraborti R. Ethnic group comparisons of variables associated with ischemic heart disease. *Br Heart J*. 1978;40:789-795.

Metra M, Nodari S, Daloia A, Bontempi L, Boldi E, Deicas L. A rationale for the use of beta-blockers as standard treatment for heart failure. *Am Heart J*. 2000;139(N3. MAR):511-521.

Moorman PG, Hames CG, Tyroler HA. Socioeconomic status and morbidity and mortality in hypertensive blacks. Saunders E. (editor) *Cardiovascular Diseases in Blacks*. Philadelphia: F.A. Davis, 1991:179-94.

Mortality from congestive heart failure: United States. *Morb Mortal Wkly Rep*. 1994;43:77-81.

Moye LA, Pfeffer MA, Wun CC, Davis BR, Geltman E, Hayes D, et al. Uniformity of captopril benefit in the SAVE study: Subgroup analysis. *Eur Heart J*. 1994;15(SUPPL. B):2-8.

Mulligan IP, Fraser AG, Tirlapur V, Lewis MJ, Newcombe RG, Henderson AH. A randomized cross-over study of enalapril in congestive heart failure: haemodynamic and hormonal effects during rest and exercise. *Eur J Clin Pharmacol*. 1988;34(4):323-31.

Mulrow CD, Mulrow JP, Linn WD, Aguilar C, Ramirez G, et al. Relative efficacy of vasodilator therapy in chronic congestive heart-failure - implications of randomized trials. *JAMA*. 1988;259(N23):3422-3426.

Mylona P, Cleland JG. Update of REACH-1 and MERIT-HF clinical trials in heart failure. Cardio.net Editorial Team. *Eur J Heart Fail.* 1999;1(2):197-200.

National Heart Lung and Blood Institute National Institutes of Health. Report of the Working Group on Research in Coronary Heart Disease in Blacks. Bethesda, MD: National Institutes of Health, 1994:1-94.

The NETWORK Investigators, Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. *Eur Heart J.* 1998;19(3):481-9.

Newman TJ, Maskin CS, Dennick LG, Meyer JH, Hallows BG, Cooper WH. Effects of captopril on survival in patients with heart failure. *Am J Med.* 1988;84(3A):140-4.

Nony P, Boissel JP, Girard P, Leizorovicz A, Lievre M, Chifflet R. Relative efficacy of angiotensin converting enzyme-inhibitors on mortality of patients with congestive-heart-failure: implications of randomized trials and role of the etiology (ischemic or nonischemic) of heart-failure. *Eur Heart J.* 1992;13(N8):1101-1108.

Northridge DB, Currie PF, Newby DE, McMurray JJ, Ford M, Boon NA, et al. Placebo-controlled comparison of candoxatril, an orally active neutral endopeptidase inhibitor, and captopril in patients with chronic heart failure. *Eur J Heart Fail.* 1999;1(1):67-72.

Northridge DB, Rose E, Raftery ED, Lahiri A, Elder AT, Shaw TR, et al. A multicentre, double-blind, placebo-controlled trial of quinapril in mild, chronic heart failure. *Eur Heart J.* 1993;14(3):403-9.

Nussberger J, Fleck E, Bahrmann H, Delius W, Schultheiss HP, Brunner HR. Dose-related effects of ACE inhibition in man: quinapril in patients with moderate congestive heart failure. The Study Group on Neurohormonal Regulation in Congestive Heart Failure: Lausanne, Switzerland; Berlin, Dusseldorf, Munich, Germany. *Eur Heart J.* 1994;15 Suppl D:113-22.

O'Connor CM, Gattis WA, Zannad F, McNulty SE, Gheorghiade M, Adams KF, et al. Beta-blocker therapy in advanced heart failure: clinical characteristics and long-term outcomes. *Eur J Heart Fail.* 1999;1(1):81-8.

Olsen SL, Gilbert EM, Renlund DG, Taylor DO, Yanowitz FD, Bristow MR. Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. *J Am Coll Cardiol.* 1995;25(6):1225-31.

Oparil S, Bakir SE. Calcium antagonists in cardiovascular disease: clinical evidence from morbidity and mortality trials. *Drugs.* 2000;59(2):25-37.

Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med.* 1996;334(21):1349-55.

Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 2001;344(22):1651-8.

Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. *Circulation.* 1996;94(11):2793-9.

Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody RJ, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med.* 1993;329(1):1-7.

Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation.* 1999;100(23):2312-8.

Pahor M, Guralnik JM, Gambassi G, Bernabei R, Carosella L, Carbonin P. The impact of age on risk of adverse drug-reactions to digoxin. *J Clin Epidemiol.* 1993;46(N11):1305-1314.

Paolisso G, Gambardella A, Marrazzo G, Verza M, Teasuro P, Varricchio M, et al. Metabolic and cardiovascular benefits deriving from beta-adrenergic blockade in chronic congestive heart failure. *Am Heart J.* 1992;123(1):103-10.

Pappas G, Queen S, Hadden W, et al. The increasing disparity in mortality between socioeconomic groups in the United States, 1960 and 1986. *N Engl J Med*. 1993;329:103-9.

Parker AB, Azevedo ER, Baird MG, Smith SJ, Arnold JM, Humen DP, et al. ARCTIC: assessment of haemodynamic response in patients with congestive heart failure to telmisartan: a multicentre dose-ranging study in Canada. *Am Heart J*. 1999;138(5 Pt 1):843-8.

Pennell DJ, Ray SG, Davies G, Burgess M, Webster J, Slomka P, et al. The carvedilol hibernation reversible ischaemia trial, marker of success (CHRISTMAS) study. Methodology of a randomised, placebo controlled, multicentre study of carvedilol in hibernation and heart failure. *Int J Cardiol*. 2000;72(3):265-74.

Persson H, Rythe'n-Alder E, Melcher A, Erhardt L. Effects of beta receptor antagonists in patients with clinical evidence of heart failure after myocardial infarction: double blind comparison of metoprolol and xamoterol. *Br Heart J*. 1995;74(2):140-8.

Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327(10):669-77.

Pfeffer MA, Lamas GA, Vaughan DF, et al. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. *N Engl J Med*. 1988;319:80-100.

Pflugfelder PW, Baird MG, Tonkon MJ, DiBianco R, Pitt B. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawal in chronic heart failure: a double-blind, placebo-controlled study of quinapril. The Quinapril Heart Failure Trial Investigators. *J Am Coll Cardiol*. 1993;22(6):1557-63.

Philbin EF, DiSalvo TG. Influence of race and gender on care process, resource use, and hospital-based outcomes in congestive heart failure. *Am J Cardiol*. 1998;82:76-81.

Philbin EF, Santella RN, Rocco TA Jr. Angiotensin-converting enzyme inhibitor use in older patients with heart failure and renal dysfunction. *JAGS*. 1999;47(3):302-308.

Pitt B, Poole-Wilson P, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effects of losartan versus captopril on mortality in patients with symptomatic heart failure: rationale, design, and baseline characteristics of patients in the Losartan Heart Failure Survival Study--ELITE II. *J Card Fail*. 1999;5(2):146-54.

Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000;355(9215):1582-7.

Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997;349(9054):747-52.

Pitt B, Yusuf S, for the SOLVD Investigators. Studies of left ventricular dysfunction (SOLVD) subgroup results. *J Am Coll Cardiol*. 1992; 19:215A.

Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341(10):709-17.

Plehn JF, Krause-Steinrauf H, Anand IS, et al. Effect of race on cause-specific cardiovascular mortality in BEST. *Circulation*. 2000;102 (suppl 2)(18).

Pollock SG, Lystash J, Tedesco C, Craddock G, Smucker ML. Usefulness of bucindolol in congestive heart failure. *Am J Cardiol*. 1990;66(5):603-7.

Pouleur H. Results of the treatment trial of the studies of left ventricular dysfunction (SOLVD). The SOLVD Investigators. *Am J Cardio*. 1992;70(10):135C-136C.

Pouleur H, Rousseau MF, Melin J, Marchandise B, Schroeder E, Ahn S, et al. Studies of left ventricular dysfunction (SOLVD) - rationale, design and methods: two trials that evaluate the effect of enalapril in patients with reduced ejection fraction. *Am J Cardio.* 1990;66(3):315-322.

Pouleur H, Rousseau MF, Oakley C, Ryden L. Difference in mortality between patients treated with captopril or enalapril in the Xamoterol in Severe Heart Failure Study. *Am J Cardiol.* 1991;68(1):71-4.

Pouleur HG, Konstam MA, Udelson JE, Rousseau MF. Changes in ventricular volume, wall thickness and wall stress during progression of left ventricular dysfunction. The SOLVD Investigators. *J Am Coll Cardiol.* 1993;22(4 Suppl A):43A-48A.

Pousset F, Copie X, Lechat P, Jaillon P, Boissel JP, Hetzel M, et al. Effects of bisoprolol on heart rate variability in heart failure. *Am J Cardiol.* 1996;77(8):612-7.

Powers ER, Chiaramida A, DeMaria AN, Giles TD, Hackshaw B, Hart W, et al. A double-blind comparison of lisinopril with captopril in patients with symptomatic congestive heart failure. *J Cardiovasc Pharmacol.* 1987;9 Suppl 3:S82-8.

The Randomized Aldactone Evaluation Study (RALES) Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure *Am J Cardio.* 1996;78(8) p902-7.

Regitz-Zagrosek V, Leuchs B, Krulls-Munch J, Fleck E. Angiotensin-converting enzyme inhibitors and beta-blockers in long-term treatment of dilated cardiomyopathy. *Am Heart J.* 1995;129(4):754-61.

Remes J, Nikander P, Rehnberg S, Halinen MO, Kuikka J, Lansimies E, et al. Enalapril in chronic heart failure, a double-blind placebo-controlled study. *Annals of Clinical Research.* 1986;18(3):124-8.

Remme WJ, Krayenbuhl HP, Baumann G, Frick MH, Haehl M, Nehmiz G, et al. Long-term efficacy and safety of pimobendan in moderate heart failure. A double-blind parallel 6-month comparison with enalapril. The Pimobendan-Enalapril Study Group. *Eur Heart J.* 1994;15(7):947-56.

The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy: the randomized evaluation of strategies for left ventricular dysfunction pilot study. *Circulation.* 2000;101(4):378-84.

Richardson A, Bayliss J, Scriven AJ, Parameshwar J, Poole-Wilson PA, Sutton GC. Double-blind comparison of captopril alone against frusemide plus amiloride in mild heart failure. *Lancet.* 1987;2(8561):709-11.

Riegger GA. The effects of ACE inhibitors on exercise capacity in the treatment of congestive heart failure. *J Cardiovasc Pharmacol.* 1990;15 Suppl 2:S41-6.

Risler T, Braun U, Klarner HG, Muller-Schauenburg W, Heitkamp HC, Brilla GG, et al. [Comparison of lisinopril and captopril in treatment of severe heart failure (NYHA III-IV) in high risk patients. Preliminary results of the trial]. *Z Kardiol.* 1991;80 Suppl 2:40-3.

Rochon PA, Tu JV, Anderson GM, Gurwitz JH, Clark JP, Lau P, et al. Rate of heart failure and 1-year survival for older people receiving low-dose beta-blocker therapy after myocardial infarction. *Lancet.* 2000;356(N9230. AUG 19):639-644.

Rogers WJ, Johnstone DE, Yusuf S, Weiner DH, Gallagher P, Bittner VA, et al. Quality of life among 5,025 patients with left ventricular dysfunction randomized between placebo and enalapril: the Studies of Left Ventricular Dysfunction. The SOLVD Investigators. *J Am Coll Cardiol.* 1994;23(2):393-400.

Rouleau JL, Pfeffer MA, Stewart DJ, Isaac D, Sestier F, Kerut EK, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet.* 2000;356(9230):615-20.

Rucinska EJ. A Double Blind Placebo Controlled Study to Evaluate the Effects of Enalapril in Patients with Chronic Heart Failure. (unpublished report) 1991.

Rucinska EJ. Enalapril vs. Placebo in Previously Untreated Patients with CHF. 1991.
Rucinska EJ. Lisinopril First-Line Therapy in CHF. (unpublished report) 1991.

Rucinska EJ, Small R, Irvin J. High-risk patients treated with enalapril maleate: safety considerations. *Int J Cardiol*. (unpublished report) 1989;22(2):249-59.

Rutherford JD, Pfeffer MA, Moye LA, Davis BR, Flaker GC, Kowey PR, et al. Effects of captopril on ischemic events after myocardial infarction: Results of the survival and ventricular enlargement trial. *Circulation*. 1994;90(4 I):1731-1738.

Ryden L, Malmberg K. Benefits of ace inhibitors: what remains to be proven? *Eur Heart J Supplements*. 2000;2(NI. AUG):L3-L7.

Sanderson JE, Chan SK, Yip G, Yeung LY, Chan KW, Raymond K, et al. Beta-blockade in heart failure: a comparison of carvedilol with metoprolol. *J Am Coll Cardiol*. 1999;34(5):1522-8.

Sanderson JE, Chan SK, Yu CM, Yeung LY, Chan WM, Raymond K, et al. Beta blockers in heart failure: a comparison of a vasodilating beta blocker with metoprolol. *Heart*. 1998;79(1):86-92.

Sanderson JE, Chan WW, Hung YT, Chan SK, Shum IO, Raymond K, et al. Effect of low dose beta blockers on atrial and ventricular (B type) natriuretic factor in heart failure: a double blind, randomised comparison of metoprolol and a third generation vasodilating beta blocker. *Br Heart J*. 1995;74(5):502-7.

Schofer J, Hobuss M, Aschenberg W, Tews A. Acute and long-term haemodynamic and neurohumoral response to nisoldipine vs. captopril in patients with heart failure: a randomized double-blind study. *Eur Heart J*. 1990;11(8):712-21.

Schofield PM, Brooks NH, Lawrence GP, Testa HJ, Ward C. Which vasodilator drug in patients with chronic heart failure? A randomised comparison of captopril and hydralazine. *Br J Clin Pharmacol*. 1991;31(1):25-32.

Schwartz RS. Racial profiling in medical research. *N Engl J Med*. 2001;344(18):1392-3.

Scriven AJ, Lipkin DP, Anand IS, Sutton GC, Poole-Wilson PA. A comparison of hemodynamic effects of one-month oral captopril and enoximone treatment for severe congestive heart failure. *Am J Cardiol*. 1987;60(5):68C-71C.

Scriven AJ, Lipkin DP, Anand IS, Sutton GC, Poole-Wilson PA. Double-blind, randomised, cross-over comparison of oral captopril and enoximone added to diuretic treatment in patients with severe heart failure. *J Cardiovasc Pharmacol*. 1988;11(1):45-50.

Seedat YK. Is the pathogenesis of hypertension different in black patients? *J Hum Hypertens*. 1996;10 Suppl 3:S35-7.

Seedat YK. Ethnicity, hypertension, coronary heart disease and renal diseases in South Africa. *Ethn Health*. 1996;1(4):349-57.

Seedat YK. The prevalence of hypertension and the status of cardiovascular health in South Africa. *Ethn Dis*. 1998;8(3):394-7.

Seedat YK. Hypertension in black South Africans. *J Hum Hypertens*. 1999;13(2):96-103.

Seedat YK. Hypertension in developing nations in sub-Saharan Africa. *J Hum Hypertens*. 2000;14(10-11):739-47.

Seneviratne B, Moore GA, West PD. Effect of captopril on functional mitral regurgitation in dilated heart failure: a randomised double blind placebo controlled trial. *Br Heart J*. 1994;72(1):63-8.

Shanes JG, Wolfkiel C, Ghali J, Dierenfeldt BJ, Kondos GT, Bauman JL. Acute hemodynamic effects of pindolol and propranolol in patients with dilated cardiomyopathy: relevance of intrinsic sympathomimetic activity. *Am Heart J*. 1988;116(5 Pt 1):1268-75.

Sharpe DN, Murphy J, Coxon R, et al. Enalapril in patients with chronic heart failure: a placebo controlled randomized double-blind study. *Circulation*. 1984;70:271-8.

Sharpe DN, Murphy J, Smith H, et al. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet*. 1988:255-9.

Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardio*. 1996;77(11):1017-20.

Sigurdsson A, Amtorp O, Gundersen T, Nilsson B, Remes J, Swedberg K. Neurohormonal activation in patients with mild or moderately severe congestive heart failure and effects of ramipril. The Ramipril Trial Study Group. *Br Heart J.* 1994;72(5):422-7.

Silke B, Tennet H, Fischer-Hansen J, Keller N, Heikkila J, Salminen K. A double-blind, parallel-group comparison of flosequinan and enalapril in the treatment of chronic heart failure. *Eur Heart J.* 1992;13(8):1092-100.

Simarro E, Rodriguez MA, Bayon J, Lastra JA, Prieto P, Suarez G, et al. [The effect of gallopamil and propranolol in patients with ischemic cardiopathy and moderate depression of ventricular function]. *Rev Esp Cardiol.* 1995;48(11):741-5.

Simpson K, Jarvis B. Lisinopril: a review of its use in congestive heart failure. *Drugs:*2000;59(5):1149-67.

Singh V, Christiana J, Frishman WH. How to use calcium antagonists in hypertension: putting the JNC-VI guidelines into practice. Joint National Committee for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Drugs.* 1999;58(4):579-87.

The SOLVD Investigators. Studies of left ventricula dysfunction (SOLVD) rationale, design and methods: two trials that evaluate the effect of enalapril in patients with reduced ejection fraction. *Am J Cardiol.* 1990;66:315-22.

The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med.* 1991;325(5):293-302.

Spargias KS, Hall AS, Greenwood DC, Ball SG. beta blocker treatment and other prognostic variables in patients with clinical evidence of heart failure after acute myocardial infarction: evidence from the AIRE study. *Heart.* 1999;81(1):25-32.

Stamler J, Rhomberg P, Schonberger JA. Multivariate analysis of the relationship of the seven variables to blood pressure. *J Chron Dis.* 1975;28:527-548.

Suwa M, Ito T, Otake Y, Moriguchi A, Hirota Y, Kawamura K. Comparison of the therapeutic effects of the beta-blocking agent bisoprolol and the calcium-blocking agent diltiazem in patients with heart failure due to dilated cardiomyopathy. *Jpn Circ J.* 1996;60(10):767-73.

Swedberg K. Effects of ace-inhibition on renal-function in severe congestive-heart-failure. *Zeitschrift Fur Kardiologie.* 1991;80(S2):50-54.

Swedberg K, Amtorp O, Gundersen T, et al. Is maximal exercise testing a useful method to evaluate treatment of moderate heart failure? *Circulation*. 1991;57:226.

Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. *Circulation*. 1990;82(5):1730-6.

Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med.* 1992;327(10):678-84.

Swedberg K, Kjekshus J. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *Am J Cardio.* 1988;62(2):60A-66A.

Swedberg K, Kjekshus J, Snapinn S. Long-term survival in severe heart failure in patients treated with enalapril. Ten year follow-up of CONSENSUS I. *Eur Heart J.* 1999;20(2):136-9.

Texter M, Lees RS, Pitt B, Dinsmore RE, Uprichard AC. The QUinapril Ischemic Event Trial (QUIET) design and methods: evaluation of chronic ACE inhibitor therapy after coronary artery intervention. *Cardiovasc Drugs Ther.* 1993;7(2):273-82.

Timmis AD, Bojanowski LM, Najm YC, Nelson DJ, Gosling RG. Captopril versus placebo in congestive heart failure: effects on oxygen delivery to exercising skeletal muscle. *Eur Heart J.* 1987;8(12):1295-304.

Tonkon M, Awan N, Niazi I, Hanley P, Baruch L, Wolf RA, et al. A study of the efficacy and safety of irbesartan in combination with conventional therapy, including ACE inhibitors, in heart failure. Irbesartan Heart Failure Group. *Int J Clin Pract.* 2000;54(1):11-4, 16-8.

Torp-Pedersen C, Kober L, Carlsen J. Angio-converting enzyme inhibition after myocardial infarction: the Trandolapril Cardiac Evaluation Study. *Am Heart J.* 1996;132(1 Pt 2 Su):235-43.

Tsuyuki RT, McAlister FA, Teo KK. Beta-blockers for congestive heart failure: what is the current consensus? *Drugs Aging.* 2000;16(1):1-7.

Uhlir O, Dvorak I, Gregor P, Malek I, Spinarova L, Vojacek J, et al. Nebivolol in the treatment of cardiac failure: a double-blind controlled clinical trial. *J Card Fail.* 1997;3(4):271-6.

Uprichard A. A 12-Week Double Blind, Placebo Controlled Study to Determine the Efficacy and Safety of Orally Administered Quinapril Hydrochloride in Patients with Congestive Heart Failure (unpublished report) 1994.

Uprichard A. A 16-week Double Blind, Placebo-Randomized Placebo Controlled Multicenter Trial to Evaluate the Effects of Withdrawal of Quinapril Hydrochloride on Exercise Tolerance in Patients with Mild to Moderate Congestive Heart Failure. (unpublished report) 1994.

Uprichard A. An 18-Week Double Blind, Optional Titration, Multicenter Study to Compare the Efficacy and Safety of Orally Administered Quinapril Hydrochloride with Captopril and Placebo in Patients with Congestive Heart Failure. (unpublished report) 1994.

Van den Heuvel AF, Van Gilst WH, Van Veldhuisen DJ, De VriesRJM, Dunselman PHJM, Kingma JH. Long-term anti-ischemic effects of angiotensin-converting enzyme inhibition in patients after myocardial infarction. *J Am Coll Cardiol.* 1997;30(2):400-405.

van der Does R, Hauf-Zachariou U, Pfarr E, Holtbrugge W, Konig S, Griffiths M, et al. Comparison of safety and efficacy of carvedilol and metoprolol in stable angina pectoris. *Am J Cardiol.* 1999;83(5):643-9.

van Veldhuisen DJ, Genth-Zotz S, Brouwer J, Boomsma F, Netzer T, Man, Veld AJ, et al. High-versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril. *J Am Coll Cardiol.* 1998;32(7):1811-8.

Vedin A, Wikstrand J, Wilhelmsson C, Wallentin I. Left ventricular function and beta-blockade in chronic ischaemic heart failure. Double-blind, cross-over study of propranolol and penbutolol using non-invasive techniques. *Br Heart J.* 1980;44(1):101-7.

Viscoli CM, Horwitz RI, Singer BH. Beta-blockers after myocardial infarction: Influence of first-year clinical course on long-term effectiveness. *Ann Intern Med.* 1992;118(2):99-105.

Vitovec J, Spinar J. First-dose hypotension after angiotensin-converting enzyme (ACE) inhibitors in chronic heart failure: a comparison of enalapril and perindopril. Slovak Investigator Group. *Eur J Heart Fail.* 2000;2(3):299-304.

Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet.* 1993;342(8885):1441-6.

Watanabe H, Kakihana M, Ohtsuka S, Sugishita Y. Randomized, double-blind, placebo-controlled study of carvedilol on the prevention of nitrate tolerance in patients with chronic heart failure. *J Am Coll Cardiol.* 1998;32(5):1194-200.

Weber KT, Kinasewitz GT, West JS, et al. Long-term vasodilator therapy with trimazosin in chronic cardiac failure. *N Engl J Med.* 1980;303:242-250.

Webster MWI, Fitzpatrick MA, Hamilton EJ, et al. Effects of Enalapril on clinical status, biochemistry, exercise performance and haemodynamics in heart failure. *Drugs.* 1985;30(Suppl 1):74-81.

Wedel H, DeMets D, Deedwania P, et al. Challenges of subgroup analyses in multinational clinical trials: Experiences from the MERIT-HR trial. *Am Heart J.* 2001;142:502-11.

Weedle PB, Poston JW, Parish PA. The use of digoxin in 55 residential homes for elderly people. *Postgraduate Medical Journal.* 1988;64(N750):292-296.

Weir MR, Gray JM, Paster R. Differing mechanisms of action in angiotensin-converting enzyme inhibition in black and white hypertensive patients. *Hypertension.* 1995;25:124-30.

Widimsky J, Kremer HJ, Jerie P, Uhlir O. Czech and Slovak spirapril intervention study (CASSIS). A randomized, placebo and active-controlled, double-blind multicentre trial in patients with congestive heart failure. *European J Clin Pharm.* 1995;49(1-2):95-102.

Wiklund I, Swedberg K. Some methodological problems in analyzing quality of life data in severe congestive heart failure patients. *JCRP* 1991;5(3):265-273.

Wiklund I, Waagstein F, Swedberg K, Hjalmarsson A. Quality of life on treatment with metoprolol in dilated cardiomyopathy: results from the MDC trial. Metoprolol in Dilated Cardiomyopathy trial. *Cardiovasc Drugs Ther.* 1996;10(3):361-8.

Williams DR. Socioeconomic differentials in health: a review and redirection. *Soc Psychol Q.* 1990;53:81-99.

Wisenbaugh T, Katz I, Davis J, Essop R, Skoularigis J, Middlemost S, et al. Long-term (3-month) effects of a new beta-blocker (nebivolol) on cardiac performance in dilated cardiomyopathy. *J Am Coll Cardiol.* 1993;21(5):1094-100.

Witchitz S, Cohen-Solal A, Dartois N, Weisslinger N, Juste K, Darmon J Y. Treatment of heart failure with celiprolol, a cardioselective beta blocker with beta-2 agonist vasodilatory properties. The CELICARD Group. *Am J Cardio.* 2000;85(12):1467-71.

Wood AJJ. Racial differences in the response to drugs - pointers to genetic differences. *N Eng J Med.* 2001;344(18):1393-6.

Woodley SL, Gilbert EM, Anderson JL, O'Connell JB, Deitchman D, Yanowitz FG, et al. Beta-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. *Circulation.* 1991;84(6):2426-41.

Wright JT Jr, Kusek JW, Toto RD, Lee JY, Agodoa LY, Kirk KA, et al. Design and baseline characteristics of participants in the African American Study of Kidney Disease and Hypertension (AASK) Pilot Study. *Control Clin Trials.* 1996;17(4 Suppl):3S-16S.

Xu C, Weifeng S, Mingzhou L, Lansheng G. Beneficial effects of captopril on prognosis in elderly patients with acute myocardial infarction. *Chin Med Sci J.* 1998;13(2):107-111.

Xu H, Sun M, Zhou H. [Changes of plasma endothelin-1 in patients with congestive heart failure and the influence of metoprolol]. *Hunan I Ko Ta Hsueh Hsueh Pao.* 1998;23(5):467-9.

Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Bristow MR, Cohn JN, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N Engl J Med.* 2001;344(18):1358-65.

Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Lukas MA, Young ST. Response of black heart failure patients to carvedilol [abstract]. *J Am Coll Cardiol.* 1997;29:284A.

Young JB, Gheorghiade M, Uretsky BF, Patterson JH, Adams KF Jr. Superiority of "triple" drug therapy in heart failure: insights from the PROVED and RADIANCE trials. Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin. Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme. *J Am Coll Cardiol.* 1998;32(3):686-92.

Yusuf S. Reduced mortality and morbidity with the use of angiotensin-converting enzyme inhibitors in patients with left ventricular dysfunction and congestive heart failure. *Herz.* 1993;18 Suppl 1:444-8.

Yusuf S. Phase I results of the randomized evaluation of left ventricular dysfunction (RESOLVD) trial. *Am J Managed Care.* 1998;4(7 SUPPL.):S380-S383.

Yusuf S, Garg R, Mcconachie D. Effect of angiotensin-converting enzyme-inhibitors in left-ventricular dysfunction - results of the studies of left-ventricular dysfunction in the context of other similar trials. *J Cardiovasc Pharmacol.* 1993;22(S9):S28-S35.

Yusuf S, Lonn E, Bosch J, Gerstein H. Summary of randomized trials of angiotensin converting enzyme inhibitors. *Clinical and Experimental Hypertension*. 1999;21(N5-6. JUL-AUG):835-845.

Yusuf S, Nicklas JM, Timmis G, Breneman G, Jafri SM, Duvernoy WFC, et al. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med*. 1992;327(10):685-691.

Yusuf S, Peto R, Lewis J, et al. Beta-blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis*. 1985;27:335-71.

Yusuf S, Phil D, Sleight P, Pogue J, Bosch J, Davies R, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342(N3. JAN 20):145-153.

Zannad F, Chati Z, Guest M, Plat F. Differential effects of fosinopril and enalapril in patients with mild to moderate chronic heart failure. Fosinopril in Heart Failure Study Investigators. *Am Heart J*. 1998;136(4 Pt 1):672-80.

Ziesche S, Rector TS, Cohn JN. Interobserver discordance in the classification of mechanisms of death in studies of heart failure. *J Cardiac Failure*. 1995;1(2):127-132.

Zwehl W, Rucinska E, for Lisinopril Chronic Heart Failure Investigators. Long-term effects of lisinopril in patients with chronic heart failure: a multicenter, placebo-controlled trial. Nicholls MG (ed). *A Focus on the Clinical Effects of a Long Acting ACE-Inhibitors/Heart Failure*. New York, NY: Raven Press, 1990:31-40.

Evidence Table 1. ACE Inhibitor - Accepted Articles

Author, Date	Drug Studied CHF Defined Study population	Sample	Followup	Data reported for specific subpop/ comorb	Data may be at patient level for specific subpop/ comorb	Study name
(Pitt B, 1992)	enalapril Systolic dysfunction Both sympt and asympt patients	6797	NR	NR	Black patients Very old (Age 80+) patients Nursing home patients	SOLVD
(Yusuf S, 1992)	enalapril Systolic dysfunction Post MI and reduced LVEF	4228	NR	Diabetic patients	Black patients Female patients	SOLVD
(The SOLVD Investigators, 1991)	enalapril Systolic dysfunction Symptomatic patients	2569	NR	NR	Black patients Diabetic patients	SOLVD
(Moye LA, 1994)	captopril Systolic dysfunction Asymptomatic patients	2231	2 yr	Black patients Female patients Diabetic patients	No subpopulations	SAVE
(Pfeffer MA, 1992)	captopril Systolic dysfunction Post MI and reduced LVEF	2231	NR	NR	Very old (Age 80+) patients Female patients Diabetic patients	SAVE
(Ball SG, 1993)	ramipril CHF unspecified Symptomatic patients	2006	NR	NR	Female patients Diabetic patients	AIRE
(Cleland JG, 1997)	ramipril CHF unspecified Symptomatic patients	2006	NR	NR	No subpopulations	AIRE
(Exner DV, 2000)	enalapril Systolic dysfunction Symptomatic patients	1996	NR	Black patients	NR	SOLVD

Evidence Table 1. ACE Inhibitor-Accepted Articles (continued)

Author, Date	Drug Studied CHF Defined Study population	Sample	Followup	Data reported for specific subpop/ comorb	Data may be at patient level for specific subpop/ comorb	Study name
(Exner DV, 2001)	enalapril Systolic dysfunction Both sympt and asympt patients	1996	NR	Black patients	No subpopulations	SOLVD
(Kober L, 1995)	trandolapril Systolic dysfunction Symptomatic patients	1749	NR	NR	Very old (Age 80+) patients Female patients Diabetic patients	TRACE
(Torp-Pedersen C, 1996)	trandolapril Systolic dysfunction Symptomatic patients	1749	NR	Diabetic patients Renal failure patients	Female patients	TRACE
(Ambrosioni E, 1995)	zofenopril Systolic dysfunction Asymptomatic patients	1556	NR	Diabetic patients	Female patients None	SMILE
(Hall AS, 1997)	ramipril CHF unspecified Symptomatic patients	603	NR	NR	Female patients Diabetic patients	AIRE
(Bulpitt CJ, 1998)	captopril, cilazapril CHF unspecified Symptomatic patients	367	12 wk	NR	Very old (Age 80+) patients Female patients	Cilazapril/Captopril Multicentre Group
(Captopril-Digoxin Multicenter Research Group, 1988)	captopril Systolic dysfunction Symptomatic patients	300	6 mo	NR	Very old (Age 80+) patients Female patients	Captopril-Digoxin Multicenter Research Group
(Swedberg K, 1999)	enalapril Systolic dysfunction Symptomatic patients	253	NR	NR	Female patients	CONSENSUS

Evidence Table 1. ACE Inhibitor - Accepted Articles (continued)

Author, Date	Drug Studied CHF Defined Study population	Sample	Followup	Data reported for specific subpop/ comorb	Data may be at patient level for specific subpop/ comorb	Study name
(Kjekshus J, 1989)	enalapril Systolic dysfunction Symptomatic patients	253	NR	Renal failure patients	Very old (Age 80+) patients Female patients Diabetic patients	CONSENSUS
(CONSENSUS, 1987)	enalapril CHF unspecified Symptomatic patients	253	NR	NR	Female patients Diabetic patients	CONSENSUS
(Jerie P, 1997)	spirapril CHF unspecified Symptomatic patients	248	12 wk	NR	Female patients	CASSIS
(Widimsky J, 1995)	spirapril Systolic dysfunction Symptomatic patients	248	12 wk	NR	Female patients Diabetic patients	CASSIS
(van Veldhuisen DJ, 1998)	imidapril Systolic dysfunction Symptomatic patients	244	12 wk	NR	Female patients	
(Brown EJ Jr, 1995)	fosinopril Systolic dysfunction Symptomatic patients	241	24 wk	NR	Black patients Female patients	Fosinopril Heart Failure Study Group
(Gustafsson I, 1999)	trandolapril Systolic dysfunction Symptomatic patients	237	NR	Diabetic patients	Female patients	TRACE
(Pflugfelder PW, 1993)	quinapril Systolic dysfunction Symptomatic patients	224	16 wk	NR	Female patients	

Evidence Table 1. ACE Inhibitor - Accepted Articles (continued)

Author, Date	Drug Studied CHF Defined Study population	Sample	Followup	Data reported for specific subpop/ comorb	Data may be at patient level for specific subpop/ comorb	Study name
(Gundersen T, 1995)	ramipril Systolic dysfunction Symptomatic patients	223	12 wk	NR	Female patients	Ramipril Multicentre Study
(Giles TD, 1990)	lisinopril CHF unspecified Symptomatic patients	193	12 wk	NR	No subpopulations	lisinopril HF group
(Kleber FX, 1992)	captopril CHF unspecified Symptomatic patients	170	NR	NR	Female patients	Munich Mild Heart Failure
(Ghose JC, 1993)	captopril CHF unspecified Symptomatic patients	153	6 mo	Other	Female patients	
(Barabino A, 1991)	captopril CHF unspecified Symptomatic patients	150	NR mo	Nursing home	Very old (Age 80+) patients Nursing home patients	
(Chalmers JP, 1987)	lisinopril CHF unspecified Symptomatic patients	130	12 wk	NR	Black patients Female patients	
(Newman TJ, 1988)	captopril Systolic dysfunction Symptomatic patients	105	NR	NR	Black patients Female patients	Captopril Multicenter Research Group
(Magnani B , 1988)	captopril CHF unspecified Symptomatic patients	94	6 mo	NR	Female patients	

Evidence Table 1. ACE Inhibitor - Accepted Articles (continued)

Author, Date	Drug Studied CHF Defined Study population	Sample	Followup	Data reported for specific subpop/ comorb	Data may be at patient level for specific subpop/ comorb	Study name
(Magnani B, 1986)	captopril CHF unspecified Symptomatic patients	94	6 mo	NR	Female patients	
(Kleber FX, 1987)	captopril CHF unspecified Symptomatic patients	59	NR	NR	NR	
(Keren G, 1994)	captopril Systolic dysfunction Symptomatic patients	50	1 yr	NR	Female patients	
(Pouleur HG, 1993)	enalapril Systolic dysfunction Asymptomatic patients	49	12 mo	NR	Female patients	SOLVD
(Sharpe DN, 1984)	enalapril CHF unspecified Symptomatic patients	36	3 mo	NR	Very old (Age 80+) patients	
(Bussmann WD, 1987)	captopril CHF unspecified Symptomatic patients	23	6 mo	NR	No subpopulations	
(Creager MA, 1985)	enalapril Systolic dysfunction Symptomatic patients	23	12 wk	NR	NR	

Evidence Table 2. Beta-Blockers- Accepted Articles

ID	Drug Studied CHF Defined Study population	Sample	Followup	Data reported for specific subpop/ comorb	Data may be at patient level for specific subpop/ comorb	Study name
(Hjalmarson A, 1999)	metoprolol Systolic dysfunction Symptomatic patients	3991	NR	Female patients Diabetic patients	Black patients	MERIT-HF
(Hjalmarson A, 2000)	metoprolol Systolic dysfunction Symptomatic patients	3991	NR	Female patients Diabetic patients	Black patients	MERIT-HF
(Wedel H, 2001)	metoprolol Systolic dysfunction Symptomatic patients	3991	NR	Black patients Female patients Diabetic patients	Black patients Female patients	MERIT-HF
(Plehn JF, 2000)	bucindolol Systolic dysfunction Symptomatic patients	2708	NR	Black patients	NR	BEST
(The Beta-Blockers Evaluation of Survival Trial Investigators (BEST, 2001)	bucindolol Systolic dysfunction Symptomatic patients	2708	NR	Black patients Female patients Diabetic patients	Black patients Female patients	BEST
(CIBIS II, 1999)	bisoprolol Systolic dysfunction Symptomatic patients	2647	NR	NR	Female patients	CIBIS
(Erdmann E, 2001)	bisoprolol Systolic dysfunction Symptomatic patients	2647	NR	Female patients Diabetic patients Renal failure patients	NR	CIBIS
(Packer M, 2001)	carvedilol Systolic dysfunction Symptomatic patients	2289	NR	Female patients	Female patients	US Carvedilol HF Study
(Packer M , 1996)	carvedilol Systolic dysfunction Symptomatic patients	1094	NR	Female patients	NR	US Carvedilol HF Study
(Yancy CW, 2001)	carcedelol Systolic dysfunction Symptomatic patients	1094	NR	Black patients	No subpopulations	US Carvedilol HF Study

Evidence Table 2. Beta-Blockers- Accepted Articles (continued)

ID	Drug Studied CHF Defined Study population	Sample	Followup	Data reported for specific subpop/ comorb	Data may be at patient level for specific subpop/ comorb	Study name
(Yancy CW, 1997)	carvedilol Systolic dysfunction Symptomatic patients	1025	NR	Black patients	NR	US Carvedilol HF Study
(CIBIS Investigators, 1994)	bisoprolol Systolic dysfunction Symptomatic patients	641	NR	NR	Female patients	CIBIS
(Eicchorn EJ, 2000)	bucindolol Systolic dysfunction Symptomatic patients	627	NR	Black patients	NR	BEST
(The RESOLVD Investigators 2000)	metoprolol Systolic dysfunction Symptomatic patients	426	24 wk	NR	Black patients Female patients Diabetic patients	RESOLVD
(Australia/New Zealand Heart Failure Research Collaborative Group, 1997)	carvedilol Systolic dysfunction Symptomatic patients	415	NR	NR	Female patients	Australia/ NZ HF Research Group
(Waagstein F, 1993)	metoprolol Systolic dysfunction Symptomatic patients	383	NR	NR	Female patients	Metoprolol in Dilated Cardiomyopathy
(Colucci WS, 1996)	carcedilol Systolic dysfunction Symptomatic patients	366	NR	Black patients Other patients Very old (Age 80+) patients	No subpopulations	US Carvedilol HF Study
(Bristow MR, 1996)	carcedilol Systolic dysfunction Symptomatic patients	345	NR	NR	Black patients Very old (Age 80+) patients	Mocha investigation
(Packer M, 1996)	carvedilol Systolic dysfunction Symptomatic patients	278	6 mo	Female patients	Female patients	PRECISE
(Herlitz J, 1997)	metoprolol CHF unspecified Post MI and reduced LVEF	262	NR	NR	Female patients Diabetic patients	Goteborg Metoprolol Trial

Evidence Table 2. Beta-Blockers- Accepted Articles (continued)

ID	Drug Studied CHF Defined Study population	Sample	Followup	Data reported for specific subpop/ comorb	Data may be at patient level for specific subpop/ comorb	Study name
(Cice G, 2000)	carvedilol Systolic dysfunction Symptomatic patients	168	6 mo	NR	Female patients	
(Bristow MR, 1994)	bucindolol Systolic dysfunction Symptomatic patients	139	12 wk	NR	Female patients	
(Witchitz S, 2000)	celiprolol Systolic dysfunction Symptomatic patients	132	1 yr	NR	Female patients	Celicard
(Cohn JN, 1997)	carvedilol Systolic Dysfunction Symptomatic patients	131	6 mo	NR	Black patients Very old (Age 80+) patients Female patients	US Carvedilol HF Study
(Doughty RN, 2000)	carvedilol Systolic dysfunction Symptomatic patients	119	6 mo	NR	Female patients None	Australia/ NZ HF Research Group
(Krum H, 1995)	carvedilol Systolic dysfunction Symptomatic patients	56	NR	NR	Female patients	
(Genth-Zotz S, 2000)	metoprolol Systolic dysfunction Symptomatic patients	52	6 mo	NR	Female patients	MIC
(Anderson JL, 1985)	metoprolol Systolic dysfunction Symptomatic patients	50	NR	NR	Female patients	
(Fisher ML, 1994)	metoprolol Systolic dysfunction Symptomatic patients	50	6 mo	NR	Female patients Diabetic patients	
(Woodley SL, 1991)	bucindolol Systolic dysfunction Symptomatic patients	49	12 wk	NR	Very old (Age 80+) patients	
(Andersson B, 1994)	metoprolol Systolic dysfunction Symptomatic patients	41	6 mo	NR	Very old (Age 80+) patients	

Evidence Table 2. Beta-Blockers- Accepted Articles (continued)

ID	Drug Studied CHF Defined Study population	Sample	Followup	Data reported for specific subpop/ comorb	Data may be at patient level for specific subpop/ comorb	Study name
(Gilbert EM, 1990)	bucindolol Systolic dysfunction Symptomatic patients	24	3 mo	NR	Female patients	
(Eichhorn EJ, 1994)	metaprolol Systolic dysfunction Symptomatic patients	24	3 mo	NR	Black patients	
(Wisenbaugh T, 1993)	nebivolol Systolic dysfunction Symptomatic patients	24	3 mo	NR	Very old (Age 80+) patients	
(Cucchini F, 1988)	metoprolol Systolic dysfunction Symptomatic patients	20	6 mo	NR	Female patients	

Evidence Table 3. ACE Inhibitor Studies Contributing to the Meta-Analysis

Study Name	Author Date Add'l Articles	Mean Treatment Duration	Patient Level Data	ARM #	N	Drug
AIRE	Hall, 1991	15 months		1	982	placebo
AIRE Study Investigators, 1993	Cleland, 1997			2	1004	ramipril
ID #00098	Hall, 1997					
	Spargias, 1998					
CONSENSUS	Swedberg, 1988	188 days	X	1	126	placebo
CONSENSUS Trial Study Group, 1987	Kjekshus, 1989			2	127	enalapril
ID #00128	Eriksson, 1990					
	Swedberg, 1990					
	Ljungman, 1992					
	Swedberg, 1999					
SAVE	Moyé, 1994	42 months		1	1112	placebo
Pfeffer, 1992	Rutherford, 1994			2	1113	captopril
ID #00101	Hager, 1998					
SMILE	Borghi, 1996	6 weeks		1	784	placebo
Ambrosioni, 1995	Ambrosioni, 1994			2	772	zofenopril
ID #00065	Boghi, 1999					

Evidence Table 3. ACE Inhibitor Studies Contributing to the Meta-Analysis (continued)

Study Name	Author Date Add'l Articles	Mean Treatment Duration	Patient Level Data	ARM #	N	Drug
SOLVD-prevention Yusuf, 1992 ID #00072	The SOLVD Invesigators, 1990 The SOLVD Investigators, 1991 Hood, 1991 Pitt, 1992 Konstam, 1992 Bangdiwala, 1992 Johnstone, 1992	37 months	X	1 2	2117 2111	placebo enalapril
SOLVD-treatment Yusuf, 1991 ID #00075	Pouleur, 1992 Pouleur, 1993 Rogers, 1994 Benedict, 1996 Konstam, 1996 Kostis, 1996 Shindler, 1996 Dries, 1999 Knight, 1999 Exner, 2000 Exner, 2001 Bourassa, 1993	41 months	X	1 2	1283 1284	placebo enalapril
TRACE Kober, 1995 ID #00094	Kober, 1996 Torp-Pedersen, 1996 Gustafsson, 1999	varied	X	1 2	873 876	placebo trandolapril

Evidence Table 4. Beta-Blocker Studies Contributing to the Meta-Analysis

Study Name	Author Date Add'l Articles	Mean Treatment Duration	Patient Level Data	ARM #	N	Drug
BEST The Beta-Blocker Evaluation of Survival Trial Investigators, 2001 ID #00439	Plehn, 2000 Eichhorn, 2000 The BEST Steering Cmte., 1995	2 years		1	1354	placebo
				2	1354	bucindolol
CIBIS CIBIS Investigators, 1999 ID #0006	CIBIS Investigators and Cmtes., 1994 Pousset, 1996 Copie, 1996 Lechat, 1997 Funck-Brentano, 2000 Erdmann, 2001	1.3 years		1	1148	placebo
				2	1137	bisoprolol
COPERNICUS Packer, 2001 ID #00441		10.4 months	X	1	1133	placebo
				2	1156	carvedilol
MERIT-HF Hjalmarson, 1999 ID #0007	The Int'l Steering Cmte. On Behalf of the MERIT-HF Study Group, 1997 Goldstein, 1999 Mylona, 1999 Fagerberg, 2000 Hjalmarson, 2000 Wedel, 2001 Ghali, 2002	1 year	X	1	2001	placebo
				2	1990	metoprolol
US Carvedilol Study Packer, 1996 ID #0005	Yancy, 1997 Colucci, 1996 Yancy, 2001	6.5 months		1	398	placebo
				2	696	carvedilol

Appendix A

Date
REF # 0098/238/171/306

Name
Address
Address

Dear XX,,

The US Agency for Healthcare Research and Quality (AHRQ) has commissioned us to perform a meta-analysis on the treatment of systolic heart failure with ace-inhibitors in particular subgroups. The participating investigators on this project are, in addition to myself:

Dr. Michael Barrett	Dr. Marvin Konstam
Dr. Greg Fonarow	Dr. Michael W. Rich
Dr. Barry Greenberg	Dr. Anthony Steimle
Dr. Paul Heidenreich	Dr. Lynne Warner Stevenson
Dr. Tom Knabel	

We read with interest your articles

"*Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators"* in Lancet,

"Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators" in European Heart Journal,

"Angiotensin-converting enzyme-inhibitors, left-ventricular dysfunction, and early heart-failure" in American Journal of Cardiology, and

"Captopril in heart failure: a double-blind study of the effects on renal function" in Journal of Cardiovascular Pharmacology.

We would be very appreciative if you could assist us by providing data from your study specific to **women, persons of African descent (Blacks), diabetics, renal insufficiency, or persons 80 years of age or older**.

Name
Date

If such subgroup data are not available, we would also appreciate that information. If you have any questions regarding this request, please call me at 310-393-0411 ext. 6669 or send email to shekelle@rand.org. Thank you very much for your assistance.

Sincerely,

Paul Shekelle, MD, PhD
Director

Appendix B

Southern California Evidence-based Practice Center
CHF Screener

1. ProCite ID: _____

2. First Author: _____
(Last name of first author)

3. Reviewer Initials: _____

4. Study design: **Circle one**
   - Randomized Clinical Trial 1
   - Other ..... 9 **(STOP)**

**** If other than RCT, then STOP ****

5. How is CHF defined? **Circle one**
   - Systolic Dysfunction 1
   - CHF unspecified 2
   - Other ..... 9 **(STOP)**

6. Drug type being studied: **Circle one**
   - Beta-Blockers 1
   - Ace Inhibitors 2
   - Other ..... 9 **(STOP)**

7. Population(s) being studied: **Check all that apply**

African/ African-American	☐	Very Old (Age 80+)	☐
Hispanic	☐	Nursing Home	☐
Asian	☐	Veterans	☐
Other ethnic/ racial minority	☐	Low Income	☐
Women	☐	Other	☐
		None of the above	☐

8. Comorbidites: **Check all that apply**
   - Diabetes ☐
   - Renal Failure ☐
   - Cognitive Dysfunction ☐
   - None of the above ☐

9. Outcomes of interest: **Check all that apply**
   - Mortality ☐
   - Other patient-centered outcomes ☐
   - Utilization ☐
   - Cost ☐
   - None of the above ☐

10. What is the total sample size of the study?

___ ___, ___ ___ ___

11. Keep this article for other reasons ☐
(good background info, previous meta-analysis, etc.)

12. What is the minimum duration of follow-up?

____ ____ _____ _____ ____ **(units)**
(please use 999 for not applicable DY, WK, MO, YR for units)

13. What is the maximum duration of follow-up?

____ ____ _____ _____ ____ **(units)**
(please use 999 for not applicable DY, WK, MO, YR for units)

14. Does the study use Kaplan Meier?
   - Yes 1
   - No 2
   - Not Applicable 9

15. What Named study does this belong to?

_____

16. What drugs were studied?

_____

17. What is the study population?
   - Symptomatic 1
   - Asymptomatic 2
   - Post MI and Reduced LVEF 3
   - Other (_____) 9

18. Is there information in the published paper that indicates data were collected although not necessarily analyzed regarding any of the following population(s): **Check all that apply**

African/ African-American	☐	Very Old (Age 80+)	☐
Hispanic	☐	Nursing Home	☐
Asian	☐	Veterans	☐
Other ethnic/ racial minority	☐	Low Income	☐
Women	☐	Other	☐
		None of the above	☐

Notes:

Southern California Evidence-based Practice Center
CHF Quality Review Form

Article ID: _____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ____of ____ Description:_____
(Enter '1of 1' if only one) (if more than one study)

1. Are the study quality data reported in this article? circle one)
   - Yes 1
   - No, it is reported in reference # _____ (skip to Q.8) 2

2. If the study was randomized, was method of randomization appropriate? (circle one)
   - Yes 1
   - No 2
   - Method not described.....8
   - Not applicable/not reported in this article 9

3. Is the study described as: (circle one)
   - Double blind 1
   - Single blind, patient 2
   - Single blind, outcome assessment 3
   - Open.....4
   - Blinding not described.....8
   - Not applicable/not reported in this article 9

4. If reported, was the method of blinding appropriate? (circle one)
   - Yes 1
   - No 2
   - Double blinding method not described.....8
   - Not applicable/not reported in this article 9

5. If study was randomized, did the method of randomization provide for concealment of allocation? (circle one)
   - Yes 1
   - No 2
   - Concealment not described.....8
   - Not applicable/not reported in this article 9

Are withdrawals (W) and dropouts (D) described? (circle one)
- Yes, reason described for **all** W and D 1
- Yes, reason described for **some** W and D 2
- Not described.....8
- Not applicable/not reported in this article 9

6. Is this a cross-over study design? (circle one)
   - Yes 1
   - No 2
   - Not described.....8
   - Not applicable/not reported in this article 9

Is there a clinical and socio-demographic characteristics table comparing the intervention arms? (circle one)
- Yes 1
- No (skip to Q.11) 2
- Not reported in this article 9

7. Are there any statistically-significant differences in the patient characteristics table? (circle one)
   - Yes 1
   - No 2
   - Not reported in this article 9

8. Were any of the following cointerventions used?

	Overall proportion	Proportions by arm			
		Placebo	Arm 2	Arm 3	Arm 4
Diuretics					
Spironolactone					
Digoxin					
Beta blockers					
ACE inhibitors/ARA					
Aspirin					

9. Enter Ns and interventions for each arm in order of first mention:

Arm	N entering	N completing	Drug name	Dose		Frequency		Mean Tx Duration	Units
	(Use Ns for mortality outcomes)		Enter code from below	Enter a # or V / ND / NA		Enter a # or V / ND / NA		Enter a # or V / ND / NA	Enter D, W, M, Y, or V / ND / NA
1	_____	_____	Placebo						
2	_____	_____	_____	_____	mg taken	_____	times per day for	_____	_____
3	_____	_____	_____	_____	mg taken	_____	times per day for	_____	_____
4	_____	_____	_____	_____	mg taken	_____	times per day for	_____	_____

Codes for Beta Blockers:		Codes for ACE inhibitors:		Other Codes:	
Bisoprolol	1	Benazepril	7	Imidapril	14	Variable	V
Bucindolol	2	Captopril	8	Quinapril	15	Not Applicable	NA
Carvedilol	3	Cilzapril	9	Ramipril	16	Not Described	ND
Celiprolol	4	Cisinopril	10	Spirapril	17		
Metoprolol	5	Delapril	11	Trancolapril	18	Day	D
Nebivolol	6	Enalapril	12	Zofenopril	19	Week	W
		Fosinopril	13			None of the above/Other	OTHER

10. If **beta-blockers**, was it one of the following studies? (check all that apply)
- Australia/NZ HF Group ❑
- BEST ❑
- CARIBE ❑
- Celicard ❑
- CIBIS ❑
- MERIT – HF ❑
- Metoprolol in Dilated Cardiomyopathy ❑
- MIC ❑
- RESOLVD ❑
- US Carvedilol Study ❑
- None of the above ❑

11. If **ace inhibitors**, was it one of the following studies? (check all that apply)
- AIRE ❑
- Captopril Multicenter Research Group ❑
- Captopril-Digoxin Multicenter Research Group ❑
- CASSIS ❑
- Cilazapril Captopril Multicentre Group ❑
- CONSENSUS ❑
- Fosinopril Heart Failure Study Group ❑
- Munich Mild Heart Failure ❑
- SAVE ❑
- SMILE ❑
- SOLVD ❑
- TRACE ❑
- None of the above ❑

12. How are mortality results presented? (check all that apply)
- Proportion ❑
- Kaplan-Meier Curve ❑
- Hazard ratio ❑
- Other (specify:_____) ❑

Appendix C

Date

Name
Address
Address
Address

Dear XX,

We are currently finishing preparation of a report on heart failure commissioned by the U.S. Agency for Healthcare Research and Quality, and are seeking peer reviewers. This report presents two analyses:

1) an assessment of the effect of beta-blockers or ACE inhibitors on mortality in women, blacks, and diabetics; by pooling the relevant data from the major published randomized trials; and

2) a cost effectiveness analysis of screening for asymptomatic left ventricular dysfunction followed with ACE inhibitor treatment.

We are hoping you will be able to be a peer reviewer of this draft report. We expect the draft report to be available in approximately two weeks, and then reviewers would have three weeks to complete their review. The Agency for Healthcare Research and Quality has agreed to have us pay an honorarium of $300 for the review.

Please fax the enclosed form to Shannon Rhodes at 310-451-6930 indicating whether or not you are willing to be a peer reviewer.

If you have any questions, please do not hesitate to contact me at 310-393-0411 ext 6669 or at Shekelle@rand.org.

Sincerely,

Paul Shekelle, MD, PhD
Director, Southern California
Evidence-based Practice Center

Southern California Evidence-based Practice Center
CHF Evidence Report
Reviewer Request Form

To: Shannon Rhodes
Phone: 310-393-0411 ext 6198

Fax Number: 310-451-6930

I, XX, am

❒ able

❒ unable

to participate as a peer reviewer of the Heart Failure Evidence Report.

REVIEW QUESTIONS TO CONSIDER AND ON WHICH YOU MAY WANT TO COMMENT ARE LISTED HERE:

OVERALL EVALUATION
Is it clear what we did? You may agree or disagree with our methods, findings or conclusions, but you should be able to understand what it is we did in order to produce this report.

QUESTION FORMULATION
Are evidence report questions well formulated and easily understandable?

STUDY IDENTIFICATION
Is there a thorough search for relevant data using appropriate resources?
Are there unbiased, explicit searching strategies that are appropriately matched to the question?

STUDY SELECTION
Are appropriate inclusion and exclusion criteria used to select articles? Are selection criteria applied in a manner that limits bias? Are efforts made to identify unpublished data, if this is appropriate? Are reasons for excluding studies from the report stated? Did we miss any crucial pieces of information in our literature search?

APPRAISAL OF STUDIES
Are important parameters (e.g. setting, study population, study design) that could affect study results systematically addressed?

DATA COLLECTION
Is there a minimal amount of missing information regarding outcomes and other variables considered key to the interpretation of results? Are efforts made to reduce bias in the data collection process?

DATA SYNTHESIS
Are important parameters, such as study designs, considered in the synthesis? Are reasonable decisions made concerning whether and how to combine the data? Is precision of results reported? Are limitations and inconsistencies of studies stated? Are limitations of the review process stated?

CONCLUSIONS (stated throughout the report)
Are conclusions supported by the data reviewed? Is evidence appropriately interpreted as inconclusive (no evidence of effect) or as showing a particular strategy did not work (evidence of no effect)? Is a summary of pertinent findings provided? Are the specific issues related to the research question addressed adequately?

RESEARCH:
Are implications for research discussed? What directions for future research would you recommend based on this report that we have not covered?

NON-CONFLICT OF INTEREST STATEMENT

Please give your name and signature and any comments necessary and return with the review in the provided FedEx package. Thank you.

Indicate here whether you have any conflicts of interest regarding the review of the Evidence Report.

I, _____, certify that I have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the Evidence Report (e.g. employment, consultancies, stock ownership, honoraria, expert testimony).

Signed,

_____

I, _____, would like to declare my conflict of interest here. See my comments below:

Signed,

_____

PAYMENT FOR SERVICES
As a reviewer for the Southern California Evidence-Based Practice Center, we will need your social security number in order to process your compensation. Please provide here:

SS# (or TAX ID) _____ - _____ - _____

Appendix D

Appendix D

Page #	Section	Reviewers' Comments	Author's Response to Comments
	General	Questions were well formulated and easily understandable. Methods were explained carefully in text. It appears as if great effort was made to exclude bias.	No response necessary
	General	I believe that this work is unique and valuable.	No response necessary
	General	I am impressed by the clarity of writing and, given the scope of the project and large amount of data/analyses, the brevity of the report.	No response necessary
	General	Goals were clearly stated.	No response necessary
v	Abstract	Avoid the statement "additional randomized controlled evidence of the effect of ACE inhibitors in women is needed." Most won't believe giving placebo to women with heart failure to be ethical.	This sentence has been deleted from the abstract.
v	Abstract	I would add a statement regarding the equivalency of both ACEI and BB in diabetics, ACEI in blacks, and BB in women.	The entire abstract has been rewritten to highlight relative risks in subgroups rather than ratio of relative risks.
v	Abstract	The manner in which some of the findings are reported is, in my opinion, misleading.	The manner of reporting the results has been changed.
18	Methods	My major concern centers on the low emphasis placed on the relative risks of the subgroups. Although the main stated objective is to assess whether the effect of medications differs by the subgroups (ratio of relative risks), the actual effect in each subgroup (relative risk) seems more clinically important.	See above comment.
19	Methods	The risk index as calculated is complex, as a positive value could reflect either that the therapy has an adverse effect in the subgroup compared to no effect or benefit in the larger population, OR that the subgroup has >= zero benefit, but less benefit than the larger population. This is discussed later in the methods somewhere, but could perhaps be highlighted early in the description of the index.	See above comment.
19	Methods	I find the ratio of relative risks difficult to interpret clinically. I would always include estimates of the relative risk - even in the abstract.	See above comment.

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
19	Methods	I had difficulty following the rationale for the initial pooling of the RRRs vs. pooling the risk ratios separately and then taking the ratio.	See above comment.
19	Methods	Confidence intervals for the RR of 0.94 for ACEI in women would be relevant.	See above comment.
37	Results	Some of the findings could be presented in a more clinically relevant and less ambitious manner. It would be helpful to present the within-subgroup pooled risks ratios and hazard ratios first, followed by the between subgroup relative risk ratios and relative hazard ratios.	See above comment.
37	Results	Within subgroup pooled risks ratios and absolute risk reductions with confidence intervals and p-values should be reported.	See above comment.
37	Results	You clearly state that a positive RRR does not necessarily exclude a mortality benefit of the drug in either subgroup. Your figures only present the RRR data, and I wonder if a table or summary figure could first show the RR for each subgroup before the RRR data is presented.	See above comment.
37	Results	I am not a fan of how the RRR was used as a summary measure. I would have rather seen the separate point estimates for treatment effect (and 95% CI) in the two comparison populations.	See above comment.
37	Results	Question is not whether a subgroup does worse than another subgroup, but whether the subgroup in question benefits from treatment.	See above comment.
37	Results	I don't think "This means that there is a 15% increase in mortality in women relative to men treated with ACEI .." is quite accurate. For instance, women may have lower mortality on placebo than men.	See above comment. This statement actually is accurate, but confusing since it concerns relative and not absolute risk. We have completely reoriented the Results section to make it more clinically understandable.
83	Future Research	The major question is not whether women benefit as much as men or blacks as much as whites. The major questions is whether these therapies are helpful, harmful, or neither in these subgroups.	See above comment.

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
i	Title	You refer to left ventricular heart failure and left ventricular heart dysfunction. These terms are not used. You could use "heart failure and left ventricular systolic dysfunction."	Done
i	Title	Possible change to "Pharmacologic management of heart failure: effects in women, black patients, and diabetics. Cost-effectiveness considerations of screening and treatment strategies."	The title has been changed to incorporate the previous comment. This title suggestion seemed to us to overweight the Cost-Effectiveness section of the report.
1	Summary	Summary seems unnecessary in light of the following report.	This section is an AHRQ requirement.
13	Overview	Although Chapter 2 nicely describes the scope of work and original potential key questions, I found myself wondering about the background / larger context of the Evidence Report. How did the ACP and other groups get involved in nominating this topic?	Groups nominate topics for evidence reports via a mechanism that can be found on AHRQ's website (www.ahrq.gov). It is beyond the scope of the Evidence Report to explain the reasons why partners nominated topics other than the information presented in the introduction.
15	Methods	Method/rationale used to formulate the first questions was clearly defined. The only concern was why the study could not have addressed whether drug efficacy varied as a function of age as originally requested.	An analysis of efficacy by age requires individual patient data, which were not available for the majority of studies. This is stated on page 18.
16	Methods	Affiliation should be UnitedHealthcare (one word)	Done
16	Methods	Search methodologies used to identify relevant data were of high quality. Search was limited to randomized clinical trials experience, and may have omitted well performed observational studies. These are sometime used as supportive data to trial subgroup analyses.	No response necessary
16	Methods	Table 1 in the Methods section doesn't help me much. Could this be deleted?	Agreed. This table has been deleted.
17	Methods	TEP members also provided names / acronyms of the major ACE inhibitor and beta-blocker trials.	The text on page 17 has been changed.

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
17	Methods	Original plan for obtaining patient level results from published and unpublished studies was strong. The strategy of limiting to largest RCTs, FDA, and published subgroup data limits the scope and generalizability somewhat by not including smaller studies, unpublished studies, etc. Overall, I feel that their prioritization decisions were pragmatic and reasonable under the circumstances.	No response necessary
17	Methods	Did all of the studies have the necessary subgroup data included in the published articles? Was the rationale to pursue patient-level data only to get more reliable data?	We pursued the necessary subgroup data from all studies but were only successful for the ones listed. The rationale was to increase statistical power by increasing sample size. However, we have added new sensitivity analyses of both ACE inhibitor and beta-blocker trials by clinical condition where possible.
18	Methods	Why are we restricted to the FDA data that is available electronically? The NDA submissions always include extensive tables of subgroups.	We were advised by the FDA that retrieving the paper records would take months and that we would have to search by hand through "hundreds" of filebooks to find the data we needed.
18	Methods	Data collection is complete as to what was sought, but not enough was sought.	What we sought and obtained was all that was possible within the resource constraints of the EPC contract.
18	Methods	I am surprised that cardiac mortality data was not obtainable for all studies. Perhaps a table presenting the proportion of studies that have the outcomes of interest (resource utilization, quality of life, mortality) could be included.	Cardiac mortality was available for most studies, but subgroup data regarding mortality were available for only the studies listed.
18	Methods	I am intrigued by the lack of response of some authors and trial groups who failed to respond to requests for information.	No response necessary
18	Methods	Dr. Marion Limacher, U. Florida, debates the equal efficacy of ACEI in women compared to men in the Wenger edited book on heart disease in women, in particular related to the SOLVD trial. Did authors contact Dr. Limacher re. this database, which must have been available to her at that time?	We contacted Dr. Limacher, who sent us a copy of her book chapter, which we have now incorporated into the report.
18	Methods	Data synthesis limitations are very difficult to overcome. The solution appears elegant.	No response necessary

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
18	Methods	Focusing on mortality alone makes it more difficult to see effects in small subgroups.	No response necessary
18	Methods	Studies are not extensively analyzed and limitations assessed.	No response necessary
18	Methods	Need to state the known limitations of meta-analysis as compared to controlled clinical trials, along with our reasons for using this method, namely the absence of sufficient N in each subgroup for most trials.	This limitation is currently stated in the introduction. We have added it again on page 18 and in the Limitations section.
18	Methods	Some meta-analyses include a score to grade the quality of the studies. Was such an approach considered in this meta-analysis?	No. The use of quality scores has not been favored since the publication of the Juni study (Juni P. JAMA. 1999;282(11):1054-60.)
18	Methods	If you excluded a study that was on the margin of inclusion, you might specifically mention such and the reasons for exclusion, to further illustrate your application of the criteria.	There were no studies at the margin for inclusion, we included all the RCTs with sample >1000.
21	Methods	From a clinical perspective, combining the data of the post-MI trials with the non post-MI trials is somewhat concerning. Yes, most patients had ASHD and were post-MI. However, ACE inhibitors were started within days of the MI in the post-MI trials and most did not have symptomatic HF.	A new sensitivity analysis was performed for the symptomatic and asymptomatic studies, and is presented on page 21.
21	Methods	I have concerns about the impact of combining the left ventricular dysfunction studies with the post-MI ones. Properties of the ACEIs that might have been important in the post-MI populations might not be as relevant in the LV dysfunction studies and vice-versa.	See above comment.
37	Results	You should note that your results on ACE inhibitors are based on a mix of trials in patients with heart failure and in patients with LV systolic dysfunction post -MI.	See above comment.
18	Methods	I found the use of "principle" for "principal" on numerous occasions to be distracting.	The text has been changed where appropriate.

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
18	Methods	The major criticism … will be the integrity of the "meta-analysis." Perhaps, in the final version, a short commentary about the benefits and detriments of this approach could be made.	A Limitation section has been added.
18	Methods	Authors limited their analysis to studies whose primary question was specific to LV dysfunction patients. Theoretically, there is a larger body of evidence regarding these treatment efficacy available from other trial populations (I.e. in hypertension, secondary prevention trials, etc.) These other trial types would have enrolled some proportion of patients with LV dysfunction and could have supplemented their patient level analyses.	This would have required more extensive requests for individual patient data that were beyond our resources for this project.
18	Methods	Data collection appears complete	No response necessary
18	Methods	Definition of "black" varies and is not a unified population.	This acknowledges what is already explained in the text on page 19. No response necessary.
19	Methods	I am familiar with the DerSimonian and Laird random effects model. By mentioning its low power to detect differences across studies and the fact that its only a one-step iterative method, are you implying that there are other methods that are "better?" Were these considered?	The low power refers to the chi-squared test of heterogeneity and is not associated with the DerSimonian and Laird random-effects model. The low power of the chi-squared test is well-known (Hedges and Olkin 1985). Thus, to fully assess and deal with possible heterogeneity between studies, our approach is to combine the knowledge gained from this statistical test with clinical knowledge about heterogeneity, and to use a random-effects model to adjust our variance estimates for any heterogeneity that might exist. The DerSimonian and Laird random-effects model is a one-step method in terms of how it estimates the between-study variance and is equivalent to applying a method of moments approach. It is generally accepted as the most appropriate choice for a random effects estimate when one is combining a group of studies and not incorporating covariates. If one fits a multivariate model, e.g., random effects meta-regression, sometimes a restricted maximum likelihood approach is used. In our experience, the two approaches (DerSimonian and Laird and restricted maximum likelihood) produce very similar between-study variance estimates.

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
19	Methods	Did you use the long-term CONSENSUS data for total survival? (published in European Journal…)	We used individual patient data from the original CONSENSUS trial. The long-term CONSENSUS data showed few patients still alive, which obscure the beneficial effect of ACE inhibitors in reducing mortality up to at least 3 years of followup.
19	Methods	I think the authors should have described the trial populations more clearly in the beginning of the report, as well as tested whether treatment response varied as a function of populations studied or etiology of LV dysfunction. For example, black patients are less likely to have ischemic etiology for their LV dysfunction. Thus, the lower benefits of BB in black patients theoretically may have been confounded by disease etiology.	This level of detail requires patient level data, which was available for a minority of studies. It is plausible that the differences we saw in race and sex groups reflect differences in effectiveness of these drugs on the etiologic differences in heart failure and this has been added to the Limitations and Future Research sections.
20	Methods	Depending on your target audience, a fuller description of the hazard ratio might be helpful.	Additional explanation added on page 20
22	Cost-effectiveness methods	The cost-effectiveness of treatment with ace inhibitors for those with LV dysfunction has been previously demonstrated. The question regarding asymptomatic screening was interesting and clinically relevant.	No response necessary
22	Cost-effectiveness methods	Overall the author did a superb job with this complex question. Hats off.	No response necessary
22	Cost-effectiveness methods	Model did not consider any therapy of LV dysfunction other than ACEI.	This is noted in the Limitations section. Currently only ACEi has been studied in a randomized trial of asymptomatic patients.
22	Cost-effectiveness methods	Model did not consider that many patients w/ LV dysfunction may need to be screened for coronary disease, which would drive up costs.	We determined "needed" treatments/tests based on randomized trial data and clinical guidelines for which only ACE inhibitors qualified. Screening for coronary disease will increase cost and likely benefits. However, the effectiveness (and cost-effectiveness) is not established and we believe such screening is not standard of care for asymptomatic patients with depressed EF.
22	Cost-effectiveness methods	Model did not consider other potential benefits of ACEI treatment on CAD, diabetes, etc (see HOPE study).	Our model applies to patients not on ACE inhibitors. The benefit observed in SOLVD is likely due in part to benefits from these groups (CAD, diabetes).

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
22	Cost-effectiveness methods	Rate of progression from asymptomatic LV dysfunction to symptomatic is based on SOLVD. It should be realized that patients in SOLVD had LV assessments for some reason, and are not equivalent to a totally random population.	This is an important limitation. Unfortunately there are no randomized treatment data from a totally random population. This is discussed in the Limitations section.
22	Cost-effectiveness methods	The actual annual event rates were assumed to be constant over the course of the patient's life. Is this assumption based on the SOLVD trials (at least over the first four years)?	We assumed constant a risk of death relative to the U.S. population. We determined the risk of death at year one for SOLVD, then the risk of death at year 2 conditional on surviving year one, etc. The average of these risks over the 4 year SOLVD trial (weighted by the number of patients in each years analysis) was used.
22	Cost-effectiveness methods	I'm a little surprised that you selected your baseline probability solely on the SOLVD trials, rather than meta-analyses-derived probabilities. Your sensitivity analyses mitigate this issue.	No response necessary
22	Cost-effectiveness methods	Are hospitalization rates and costs from years ago relevant to present day costs in a rapidly evolving field?	We agree that costs have changed, per-hospital day has increased while number of hospital days have decreased. Fortunately, our model was insensitive to the cost of heart failure treatment. This is noted in the Results section.
22	Cost-effectiveness methods	There have been several cost-effectiveness studies published. How does this one differ? What does it add?	Past cost-effectiveness studies have examined the treatment of *symptomatic* patients with ACE inhibitors. This study examines asymptomatic patients and also examines screening.
22	Cost-effectiveness methods	Why wasn't a cost-effectiveness of BB therapy considered? Was there consideration of cost-effectiveness analyses of the subgroups studies in the meta-analysis?	We limited the cost-effectiveness analyses to treatment and screening for asymptomatic patients. As yet there are no randomized trials of beta-blockers for this population. The impact of a possible additional benefit from beta-blockers on screening was evaluated with sensitivity analysis (makes screening more cost-effective). Separate cost-effectiveness analyses by race and gender was not performed.
22	Cost-effectiveness methods	Would have separated the data synthesis methods and results from that of the cost analysis.	AHRQ Evidence Report format does not allow this.

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
22	Cost-effectiveness methods	Unclear where the assumption that there will be a 2.7% incidence of asymptomatic LV dysfunction in asymptomatic individuals. The MONICA study found 1.5% incidence, and this was not a totally random population.	This is from reference 18 (McDonagh TA, Robb SD, Murdoch DR, Morton JJ, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998;351(9095):9-13.), which describes a population screening program.
22	Cost-effectiveness methods	Data about ACEI generally are not in patients on BBs, and whether there are additive effects is unknown.	Agreed. This is noted in the Limitations section.
22	Cost-effectiveness methods	Not sure what the third hypothetical cohort is - typo?	This has been corrected.
22	Cost-effectiveness methods	The use of a single cut-point for BNP is problematic. The levels appear to go up with age and are higher in females than males.	We agree that a gender- and age-specific cut-point may improve the accuracy of BNP. However the large population based studies used a single cut-point.
22	Cost-effectiveness methods	The explanation of extended dominance was difficult for me to understand. I would try to explain it using actual base numbers.	The description of extended dominance has been revised in the Results section.
27	Methods	Literature search criteria appear strong and the selection process thorough.	No response necessary
35	Results	I'm disappointed in the poor response from individual investigators for their patient-level data. Is this response rate common for such inquiries?	This response rate is substantially worse than previous experience with obtaining additional data from original authors, where a 60% response rate is typical.
37	Results	ACEI data as it relates to the issue of CAD: As there is much data indicating the benefit of ACEI for cardiac and vascular events in patients with CAD, could some of the difference be due to lower incidence of CAD in the women? Could we look at CAD women vs. CAD men, and non-CAD women vs. non-CAD men?	Unfortunately, this is not possible without more individual patient data, since this degree of subgroup analysis is not present in published reports. Also see comment above.

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
37	Results	It would be useful to present absolute risk reductions in addition to relative risk reductions. Providing absolute risk reductions would allow calculation of the "number needed to treat" to save one life.	Between-study heterogeneity is generally lower on the relative scale than on the absolute scale, so the accepted approach in meta-analysis is to pool studies on the relative scale, in this case to pool relative risks or ratios of relative risks. In order to back 1 = 1 calculate a general absolute risk reduction across studies from a pooled relative risk reduction (and thereby be able to estimate a number needed to treat (NNT)), one needs to make an assumption about what the underlying risk of the outcome is in the population. This risk varies across studies, and will vary depending on the reader's experience, clinical setting, etc. Therefore, we have provided a table (see page 47) that allows the reader to determine the absolute risk reduction and associated NNT, depending on the pooled relative risk reduction and the assumption he/she wishes to make about the underlying risk in the population.
37	Results	The presence of confounding variables in the populations could have influenced the results. Perhaps this should be addressed either by further analysis of the data or at least in the discussion of the results.	This has been added to the Limitations section.
37	Results	The omission of information regarding drug dose achieved in the various sub-group is important. Could the lesser effects of ACEIs in women and beta blockers in blacks be due to dosing?	This concern has been added to the Limitations section.
37	Results	Is there a limitation to your analyses due to their univariate nature? There are likely to be a variety of characteristics associated with specific subgroups, which may influence the response to treatment.	This has been added to the Limitations section.
39	Results	I'm struck by the possible difference between your findings and those of Exner (NEJM, 2001:1351-1357). They constructed a matching white cohort and compared with blacks in SOLVD. They found no difference in effect on mortality, but a substantial difference in the effect on hospitalization.	This has been added to the text on page 39.
38	Results	As for CAD above, could the diabetes gender groups be divided up as well, as diabetes clearly changes the impact of other risks? (add both to future research if not possible at this time)	This has been added to the Future Research section as it requires more individual patient level data than we had available.

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
39	Results	Separate meta-analyses without the BEST trials should be done and used to draw final conclusions for BBs. Bucindilol, which was used in BEST, has intrinsic sympathomimetic activity, wile the other BBs do not.	This analysis has been done.
39	Results	I would make note of the consistency or inconsistency of the Ratio of RR in Tables 7-17. RRR in Table 7 seems very consistent, while RRs on Table 17 are very inconsistent.	See above comment. This comment reflects the difference in results in BEST and has been handled by a new primary analysis that excludes BEST.
39	Results	The grouping of beta blockers as a class might have influenced the analysis particularly in regard to race. For instance, there is evidence that bucindolol lowered plasma NE levels considerably in the BEST trials and this was likely related to the potent beta-2 blocking properties of the molecule.	See above comment.
39	Results	Most of the beta blocker black data comes from one study (BEST).	See above comment.
39	Results	It looks like the BEST data are qualitatively different from the other studies. It may be that, for whatever reasons, bucindolol is less effective than metoprolol and carvedilol in heart failure.	See above comment.
39	Results	I can't help feeling there is something odd about the BEST trial. I would like to see the effect if BEST were removed from the analysis.	See above comment.
39	Results	Finding with regard to race and beta blockers is predominantly driven by the results of BEST. Without BEST, the overall results would be close to neutral. In contrast with ACE inhibitors, the widely held view for beta blockers is that there are important pharmacologic differences from agent to agent that make extrapolation of effect from one drug to another hazardous.	See above comment.
39	Results	The analysis assumes that ACEI and BBs are all the same! I am willing to assert that this is indeed the case with ACEIs, but I am not so sure that this is the case with BBs. This is a very contentious issue at the present time.	See above comment.

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
40	Cost-effectiveness results	Appeared that benefits of ACEI assumed to be same in men and women. Efficacy may differ by subgroups.	This limitation is now noted in the Limitation section.
40	Cost-effectiveness results	An important part of the heart failure population involves those with diastolic heart failure. It is not clear whether BNP would effectively detect it, and an ECG certainly may not	Because there are no therapies specifically for diastolic heart failure that have been shown effective in randomized trials we have focused our analysis on those with systolic dysfunction.
40	Cost-effectiveness results	I am aware of little data on the use of BNP to screen for LV dysfunction. The report only lists one reference.	Although there have been few studies, the one by McDonagh (Reference 18) is large and well done and we believe is sufficient to base our assumptions.
40	Cost-effectiveness results	"the model predicted… These results are similar to the findings of the SOLVD prevention study." As the SOLVD studies were used to derive the model, isn't this circular?	Yes, but it shows that we modeled what we intended to. All models should at a minimum reproduce the survival curves they were derived from.
40	Cost-effectiveness results	Cost-effectiveness analyses are very interesting and represent "new" data.	No response necessary
40	Cost-effectiveness results	The cost-effectiveness analysis results are nicely presented, although it was difficult for me to follow the Screening section.	The description of extended dominance has been revised in the Results section to make this easier to understand.
40	Cost-effectiveness results	It does not appear that sensitivity analyses were conducted to assess the importance of the proportion of patients hospitalized at the time of incident CHF diagnosis.	This was done and not reported since it had no impact on the results. This is now reported in the Results section.
40	Cost-effectiveness results	I thought the effect of using different BNP cut-offs on cost per QALY saved was fascinating and I would emphasize it more in the text- perhaps putting it into the summaries of conclusions.	We did not think this fit in the conclusions and left it in the text.
40	Cost-effectiveness results	The BNP threshold mentioned - 18 - is for a European assay. I suspect many readers will be familiar with Biosite's assay for which a comparable cutoff is around 80. Would point out which assay the 18 cut-off applies to.	This is now stated in Table 5.

Appendix D (continued)

Page #	Section	Reviewers' Comments	Author's Response to Comments
40	Cost-effectiveness results	Would like to see a greater expansion on the BNP issue. BNP is being used prematurely by clinicians to apply therapy to heart failure patients. Current trials are collecting BNP in a more concerted effort to sort out its utility for prediction of events. (See John Spertus's presentation at 2002 ACC. BNP did not predict worsening of HF symptoms.)	We chose to focus on using BNP to screen asymptomatic patients for this report. We now note in the Limitations section that the use of BNP for patients to determine therapy is a separate issue.
40	Cost-effectiveness results	Do you imply that everyone over the age of 55 should have screening BNP? You don't deal directly with the impact of risk factors and history of MI on the analysis. The majority of patients with asymptomatic LV systolic dysfunction have atherosclerotic disease as the etiology. Of course, prevalence is also age-related. A point score based on age and other factors might fine-tune a cost-effective approach to screening.	Our model applies to patients not on ACE inhibitors. The benefit observed in SOLVD is likely due in part to benefits from these groups (CAD, diabetes).
40	Cost-effectiveness results	Conclusions of the model are very interesting, and gratifyingly robust.	No response necessary
40	Cost-effectiveness results	Limitations of the model might be presented more fully. Future research (rather than limitation): the difference between patients with known CAD or history of MI and no history. The population with this known history creates a concentrated one in which the benefits of screening for low EF may be even more obvious. Conversely, patients with no known history of any cardiovascular disease may have less benefit.	We agree that it is the risk of depressed ejection fraction, not age alone, that is the prime determinant of the cost-effectiveness of screening. For populations with at least 1.5% prevalence of depressed EF, screening is a reasonable value. Further work to develop such a scoring system would be helpful to determine optimal screening candidates.

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Page #	Section	Reviewers' Comments	Author's Response to Comments
40	Cost-effectiveness results	Limitation: inevitable with the current data sets is the lack of any information on truly asymptomatic patients with no history. This should be stated clearly. It is not clear how the SOLVD patients for the prevention arm were identified, but someone had already been concerned enough to obtain a measure of LV function. We would all anticipate that patients who have never come to medical attention for cardiovascular disease would have a better outcome with asymptomatic disease than those who were already under surveillance.	This is an important limitation and is discussed in the Limitations section.
40	Cost-effectiveness results	Should be cost of BNP test less than $120 (not $170).	This error has been corrected.
40	Cost-effectiveness results	The $200 price for an echo sounds way too low.	We estimated the cost of the least expensive echocardiogram that could determine LV systolic function (no Doppler needed).
42	Cost-effectiveness results	Reference to Table 21 seems incorrect.	The reference has been corrected. (Table 19).
52	Results	Table 17 (now Table 18) - should the RRR for the US Carvedilol trials be 1.39 rather than 1.15? Figure 12 appears to place it correctly.	Thank you for pointing out this problem. The table was incorrect due a transposition of numbers. The correct RRR in the table should be 1.41, not 1.14. The confidence interval of (0.43,4.68) is correct in the table. The graph is correct.
52	Results	In Figure 12 and Table 17 the ratio of relative risks for US Carvedilol seems inconsistent - about 1.35 in the figure and 1.14 in the table.	See above comment.
57	Results	Graphs of data display relative risk of benefit between groups, as opposed to relative risk of placebo vs. Rx in the groups of interest.	No response necessary
71	Cost-effectiveness results	The sensitivity analyses Figures 19-21 are difficult to interpret and would benefit from a more detailed figure legend.	These figures and their legends have been revised.
81	Conclusions	Occasional ambiguity "Neither, however is there evidence that ACE, inhibitors help women with heart failure… The results suggest but do not prove that ACE inhibitors have a beneficial effect on mortality in women with heart failure."	This section has been rewritten.

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Page #	Section	Reviewers' Comments	Author's Response to Comments
81	Conclusions	Would recommend including a paragraph or two on how the authors view their findings being applied and to whom. For example, do the authors think that insurers will use these data to apply use of appropriate therapy as a quality measure assessment? Will CMS use for reimbursement justification?	Evidence Reports are specifically prohibited from suggesting possible practice or policy implications of the evidence.
81	Conclusions	State clearly that you are not advocating changing any treatment recommendations based on the subgroup analyses. Rather, the results should stimulate further investigation.	This section has been rewritten.
81	Conclusions	Report does not emphasize the multiple assumptions which lead to the stated conclusions.	This has been added.
81	Conclusions	There should be a Limitations section for the Cost-Effectiveness analysis and Meta-Analysis sections.	This has been added.
81	Conclusions	I am somewhat concerned about the release of some of the information such as the "not helpful" or "harmful" impression for beta-blockade in diabetic or Black patients rendered to non-scrutinizing MDs and the general public. This could have an unintended, potentially harmful effect on patients.	The Conclusions section has been rewritten to try to avoid creating this impression.
83	Future Research	The majority of beta blocker trials (except BEST) found a benefit in both blacks and whites. Is it ethical to perform further placebo controlled studies in blacks to see if this benefit is as large as in whites?	This is a question beyond the scope of the evidence report. We note that the pooled RR of mortality effect in blacks of non-BEST beta-blocker studies is not statistically significant.
83	Future Research	I am in total agreement that additional studies need to be done, in particular in the elderly and diabetic patients.	No response necessary
83	Future Research	As we move forward to screen truly asymptomatic patients, there will be some finite costs to the new diagnosis of a disease condition. This could also be mentioned as an area of future research - appropriate counseling and measurement for these costs. For patients with some other pre-existing condition, the benefit of ACEI for newly diagnosed heart failure may be diminished by those patients already on ACEI or ARB for other conditions such as HTN or diabetes.	We agree that there are unclear costs of a disease diagnosis and the need for future research is now noted. We also agree that as ACE inhibitors are more widely used, the benefits of screening will decrease.

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Page #	Section	Reviewers' Comments	Author's Response to Comments
83	Future Research	Addressing the cost-effectiveness of ACEI in women would tie in the two main methodologies of the report well.	No response necessary
83	Future Research	How would the addition of BBs to ACEI affect the cost-effectiveness of screening? Since you did not do this analysis, a statement addressing this may be helpful.	This is now stated in the Limitations section.
83	Future Research	We should also call for more controlled studies in black patients.	This clarification has been added to the Future Research section.
83	Future Research	Future work should focus on potential barriers to use of beta-blockers in patients with heart failure, including practitioner, patient, and drug-related barriers.	This has been added to the Future Research section.
83	Future Research	Future work should focus on the outcome of patients screened for heart failure with BNP and/or echocardiograms, including false positives.	This is now stated in the Future Research section.
83	Future Research	What are the prospects for answering the Original Potential Key Questions? What kind of data are required? What kind of studies?	This change has been made to the Future Research section.
83	Future Research	The implications of the findings of this project for research are understated. Perhaps add a final section "the implications, significant, and application of the findings of this project report to futures studies and trials."	We have rewritten the Future Research section to more accurately reflect the implications of our findings.
83	Future Research	The importance of outcomes other than mortality needs to be stressed.	This has been added to this section.
83	Future Research	Mortality is probably the most appropriate end-point of use. However, information regarding the development of heart failure (in the post MI and SOLVD prevention pops) and hospitalizations might be interesting to include in the analysis.	This has been added to this section.
83	Future Research	A major point that could and should be stressed in the final document is the need to consider issues related to subgroups when studies are being designed. Under-representation of female patients and minorities in clinical trials remains a problem.	This has been added to this section.

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Page #	Section	Reviewers' Comments	Author's Response to Comments
83	Future Research	Heart failure trials have not been powered to address specific questions related to gender, race, presence or absence of ischemic heart disease, and presence or absence of diabetes. Perhaps the most important message coming from this report is that greater participation in trials by these subsets is needed.	See above comment
83	Future Research	This report should spark more basic research into molecular biodynamics that characterize race, gender, and disease-specific heart failure issues.	This has been added to this section
83	Future Research	Would like to see a better developed group of suggestions for future trials to analyze these very important and relevant subgroups.	This has been done to the extent customary in AHRQ evidence reports.