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 ..... ☐
   Hispanic ..... ☐
   Asian ..... ☐
   Other ethnic/ racial minority ..... ☐
   Women ..... ☐
   Very Old (Age 80+) ..... ☐
   Nursing Home ..... ☐
   Veterans ..... ☐
   Low Income ..... ☐
   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 ..... ☐
    Hispanic ..... ☐
    Asian ..... ☐
    Other ethnic/ racial minority ..... ☐
    Women ..... ☐
    Very Old (Age 80+) ..... ☐
    Nursing Home ..... ☐
    Veterans ..... ☐
    Low Income ..... ☐
    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					

Southern California Evidence-based Practice Center
CHF Quality Review Form

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.

Appendix D (continued)

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.

Appendix D (continued)

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.

Appendix D (continued)

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.

Appendix D (continued)

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.