Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease*

Research Review Citation: Coleman CI, Baker WL, Kluger J, Reinhart K, Talati R, Quercia R, Mather J, Giovenale S, White CM. Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease. Comparative Effectiveness Review No. 18. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) Rockville, MD: Agency for Healthcare Research and Quality. October 2009. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each comparative effectiveness research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. The tables below include the responses by the authors of the review to each comment that was submitted for this draft review.

Section	Comment	Response
Executive Summary	Page ES-13: Dangling parentheses in the KQ4 discussion.	We have now fixed the dangling parentheses.
Introduction	The report makes frequent use of the term "ischemic heart disease risk equivalents" without definition (e.g., bottom of page 2). While this term may be commonplace within the clinical area, many readers will be unfamiliar with it. The term should be defined both in the text of the document and in the glossary.	We now define “ischemic heart disease risk equivalents” in the both the methods section as well as in the abbreviations section as recommended.
Introduction	I would recommend changing the title to better describe the review. "Comparative Effectiveness of "Medical Therapies" with or without ACEs or ARBs" sounds as if this review focuses on the vaguely defined "Medical Therapies" rather than ACEs and ARBs	The title has been altered as recommended.
Introduction	One assumption that should be made clear up front is that the review assumes a "class effect" in that all ARBs are treated equally and all ACEs are treated equally. I think most, but not all, providers and investigators share this assumption, but this is not explored in the review.	Thank you for this recommendation. Text has been added to the Data Synthesis portion of the Methods section of the CER to make this point clear.
Introduction	An additional assumption for much of the review is that ACEs and ARBs are likely equivalent and can be evaluated as a group (although authors appropriately present both combined and split analyses). The best studies for testing this assumption involve direct comparisons of ACEs and ARBs, and there are not many available in this review. However, there is a larger literature involving direct comparisons of ACEs and ARBs in CHF, nephropathy, and HTN and I recommend citing these reviews to support the decision to batch ACEs and ARBs together.	Text has been added to the introduction and methods regarding evidence to support the decision to batch ACEIs and ARBs together.
Introduction	Well written and comprehensive. Adding a figure about the mechanism of ACEI and ARB action may help	A figure representing the impact of ACE inhibitors and ARBs on the renin-angiotensin aldosterone system has been added as recommended.
Introduction	Different etiologies of stroke are not discussed since these could be impacted differently by therapy. Would like this expanded. (p.22 for example)	Thank you for this suggestion. Unfortunately, the included studies did not routinely report the etiology of the strokes. Thus a detailed discussion on this would not be possible.
Introduction	Atrial fibrillation is a difficult endpoint since this can be impacted by the underlying cause of atrial fibrillation only some of which may show benefit with therapy.	We agree that the etiology of atrial fibrillation in this patient population is likely multifactorial. However, previous investigations have established the benefit of ACEIs and ARBs for reducing the risk of new-onset atrial fibrillation, particularly in the heart failure population. Thus we, along with the TEP, felt that this was a relevant endpoint of interest in this population.
Introduction	Concomitant medications did not include anticoagulant use and over the counter medications.	We did not feel that anticoagulants or over the counter medications were considered a part of the standard medical therapy of patients with ischemic heart disease.

Section	Comment	Response
Introduction	Pragraph on health impact implications is repeated.	The text throughout the introduction has been reviewed to remove pertinent duplications and improve readability.
Introduction	Table 1 of ACE-I did not include lisinopril though this is one that is highly prescribed. This should be commented on. Valsartan is not listed in table, would state why.	The agents provided in Table 1 included those that were investigated in the studies included throughout the analysis. For example, valsartan was not evaluated in any of the included trials and thus was not included in Table 1.
Methods	Although the review includes a statement of the strength of evidence supporting each conclusion as well as some discussion of study quality, the link between them is not explicit. It is unclear, on first reading, how the conclusions as to strength of evidence were reached. This should be made transparent.	In the revised version of our CER, we have included a detailed description of the methods utilized in determining the strength of evidence, which can be found in the methods section on pages 9-11 of the main document. In addition, the GRADE tables (Appendix tables 41-47) include details on how each domain was assessed for all of the assessed questions and analyses. This information should help make our process more transparent to readers.
Methods	Need a clear statement defining "risk equivalents"	We have added text throughout the methods section to make it more clear exactly what populations were considered “risk equivalents” in our review, in addition to in the Abbreviations section at the end of the review.
Methods	Methods overall very well written and clearly described.	Thank You.
Methods	Why were ACE/ARB comparisons to CCB included (and not other anti-htn)? Was this a practical or theoretical decision?	We had decided *a priori* to compare ACEI/ARBs to any active therapy in the desired populations. It ended up that only comparator that met inclusion criteria was CCBs.
Methods	Was the lisinopirl-amlodipine comparison in allhat omitted? Is there any subgroup reporting of risk equivalent groups?	The ALLHAT trial was excluded for not being a study in patients with stable ischemic heart disease. Most patients had hypertension in addition to other cardiovascular risk factors.
Methods	Adding NNT or NNH to the analysis may make it better to understand the effect.	The GRADE tables, which can be found in the appendix (tables 41-47) provide absolute risk differences per 1000 for all of the outcomes and main analyses performed throughout the review.
Methods	Key question 7: I think that the authors have to make it clear that all these subgroup analysis should only be hypothesis generating and therapeutic decisions should not be based on them.	A statement has been added to the introduction to Key Question 7 as recommended.
Results	Page 48: The EPC states a strong conclusion: "Telmisartan reduces blood pressure to the same extent as other ARBs in the class and better than losartan." This conclusion is based on a simple reading of the references cited, without any critical assessment of the strength or quality of the evidence supporting it. In reaching this conclusion, the EPC violates the basic principles of the systematic review. One should not reach conclusions in the absence of a systematic review of the evidence. The statement also undermines the implicit	Thank you. We now use language that is less firm and more appropriate for the data we have. We clearly do not wish to conduct a very lengthy systematic review of the antihypertensive effects of the ARBs but do wish to convey that there is some data supporting the similar blood pressure lowering effects of almost all ARBs.

Source: www.effectivehealthcare.ahrq.gov
Published Online: March 10, 2010

Section	Comment	Response
	assumption that ARBs are interchangeable, and thus can be combined into a common meta-analysis. If there are differences between ARBs, and these differences are to be discussed within the comparative effectiveness review, then a Key Question comparing ARBs should be included in the review and systematic comparisons should be made among all of the included ARBs. Please either support the statement with the appropriate analyses, including assessments of the strength and quality of the evidence, meta-analysis of the appropriate data and inclusion of that data in the evidence tables, or remove the unsupported statement from the review.	
Results	Comment: Results should be evaluated in context of disparate populations, such as by race or income if possible.	We really wanted to conduct these analyses but as we discuss in KQ7, we cannot fully provide this data. We are hopeful that as a result of our review that further research will be conducted and that these important subgroups can be provided with this important data. We think we clearly identified types of trials or studies that can help answer questions in important subgroups such as this.
Results	Currently, only 4 clinical trials involving just 2 of the 7 available ARBs were appropriate for inclusion in this review, and data from only 1 to 3 of these trials were analyzed per Key Question. The only two ARBs with relevant evidence that were included in the report were candesartan and telmisartan. Given the paucity of data, we believe that the conclusions based on these few clinical trials should not be generalized to the entire ARB class. Conclusions may best be described using the name of the specific ARB from which the information was generated. Generalizations of concern appear throughout the review. For example, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) was the only study providing insight into Key Question 2. Based on this one trial, the investigators made the following definitive statement about ACE inhibitors and ARBs: In Key Question 2, there is direct comparative evidence from the ONTARGET trial that ACE inhibitors and ARBs provide similar benefits in major outcomes of interest in this population(page 48).	This is an excellent point. We have gone through the document and now specify which ACE inhibitors or ARBs were evaluated in order to increase transparency for the reader.
Results	We suggest the investigators consider (1) modifying the language throughout the review, where appropriate, to avoid unsubstantiated generalizations, and (2) creating a Limitations section in the report that discusses the limited applicability of the results. We acknowledge	We now specify which ACE inhibitors and ARBs were included in the different analyses throughout the executive summary and the body of the CER. We do include cautionary language and have now made that even more explicit in the revised CER. We do want to respond to the comments

Section	Comment	Response
	that the investigators do make cautionary statements about over-extending the results in several different places within the review. However, we feel that this limitation deserves a robust, consolidated discussion. Perhaps the investigators should consider stating the name of the specific ARB, instead of using the terminology ARBs when discussing the results. In addition, standard medical therapies varied greatly between the ACE inhibitor and ARB clinical trials. Most notably, the use of beta blockers, statins (or lipid-lowering agents), and diuretics was substantially higher among patients in ONTARGET and the Telmisartan Randomized Assessment Study in Angiotensin-Converting Enzyme Inhibitor-Intolerant Patients with Cardiovascular Disease (TRANSCEND) trial compared with patients in the Heart Outcomes Prevention Evaluation (HOPE) trial. Given the known benefits of beta blockers and statins on cardiovascular morbidity and mortality, the disparity in standard therapy seriously questions the appropriateness of comparing the effectiveness of ACE inhibitors and ARBs based on these specific trials.	raised about standard medical therapies. We thought that this was going to be a very important determinant of benefits and possibly results. So we did specifically evaluate this in KQ7 and the reader can use this information to determine to what extent the results are changed based on changes to standard medical therapy. We do not think that the data supports changes in beta-blocker dosing or lipid lowering therapy radically altering the effects of the ACE inhibitors or ARBs.
Results	page 20, line 43 - I don't understand the statement, "as all the trials included in key question 1 utilized intention to treat methodologies, its impact on total mortality could not be assessed"	Our intent was to evaluate the studies that either used or did not use ITT methodologies, and see if their aggregate results differed. Because all of the studies used ITT, we could not assess whether this was a factor on study results.
Results	Pg 20, line 52- Why didn't you think it reasonable to pool cardiovascular mortality and cardiac mortality? This seems like a reasonable group to combine.	We felt that cardiovascular mortality (which included death from vascular causes such as stroke) was an inherently different endpoint than cardiac death which justified them being assessed separately.
Results	Between the multiple different questions, as well as base-case analyses and subsequent subgroup analyses, there is a complicated matrix of different analyses partitioned according to population, treatment, outcomes, and differing criteria for study inclusion. While the authors should be applauded for their meticulous and exhaustive data collection analysis, I'm concerned that this level of subgroup analysis makes it harder to glean clear messages from the report. I suspect some of the information could be combined in ways that doesn't obfuscate their main findings with extensive subgroup analyses.	We appreciate this comment. In order to be transparent in our methods and results, we felt inclined to include all of the analysis we conducted. For readers that are interested in the overall results, we invite them to review the executive summary as well as the overall discussion at the end of the main document. For those readers that are interested in the more particular results, they are free to review the main document.
Results	Page 46- the authors point out in the TRANSCEND study that ACE-I performed similarly to the combination of ACE-I and ARB. They should phrase it that an ACE-I alone OR an ARB alone performed similarly to the combination. They omit the comparison between ARB and combo therapy	One of the primary objectives stated in the ONTARGET trial was to evaluate the comparative efficacy of combination ACE/ARB vs. ramipril alone. The study does not present statistical comparisons of combination ACE/ARB vs. telmisartan alone, thus we did not include a discussion of this comparison.

Section	Comment	Response
Results	Page 128, line 31: I think that comparing patient populations across trials may not be accurate and would consider deleting this.	We are suggesting that these comparisons be made within the context of an individual patient data meta-analysis which would allow access to all of the patients. We believe this could help answer a number of the questions posed in Key Question 7 in a scientifically defensible and economical manner.
Results	One of the alternate explanations of these trials have always been that the benefit is always mediated by BP reduction and thus any other medication could have the same benefit. This is in part supported by the fact that ACEI were as good As CCB in many comparison. The authors did not explain that very well and should be more emphasized in the discussion.	Thank you for this comment. We have added text to the discussion section following Key Question 1 regarding the impact of blood pressure reductions on the outcomes investigated.
Results	The authors should provide some explanations to the benefit of ACEI or ARB is a class effect or molecule specific? What about tissue specific ACE vs. non tissue specific?	Thank you for this recommendation. Text has been added to the Data Synthesis portion of the Methods section of the CER to make this point clear.
Results	Key Question 3: Key points: The authors concluded that there is larger studies are needed. That is correct. However, we also need longer follow-up duration. Four of the seven studies included here have less than 1 year follow (compared to 4-5 yearly in the first key point). Thus it is very important to detect a benefit since the event rate is usually low in patients with preserved LV function. Maybe sensitivity analysis could help here.	Thank you for this comment. We have added text to the discussion section of Key Question 3 to include the recommendation of not only larger patient numbers but also greater durations of follow-up to help better establish the benefits of ACE inhibitors or ARBs in this population.
Results	In this analysis, ACEI or ARB did not reduce the incidence of Afib. A prior meta-analysis have show different results when including patients with or without LV dysfunction. Adding this to the discussion may be helpful.	Text has been added to the discussion section following Key Question 1 regarding the impact of ACE inhibitors and ARBs on atrial fibrillation, including mention of the prior meta-analyses as recommended.
Discussion	We suggest the investigators consider including a robust discussion that addresses the variations in standard medical therapy among the ACE inhibitor and ARB trials, including the significant limitations that this disparity places on the comparative effectiveness review. Placement of this discussion within a Limitations section seems appropriate.	We specifically evaluated this in KQ7 and the reader can use this information to determine to what extent the results are changed based on changes to standard medical therapy. We do not think that the data supports changes in beta-blocker dosing or lipid lowering therapy radically altering the effects of the ACE inhibitors or ARBs.
Discussion	Discussion page 29 page 1- would beware of drawing inferences from information like “the RR was greater than 1.00 for these outcomes, but lower than 1.00 for these outcomes” particularly when there is not statistical support for meaningful differences.	These statements have been removed from the discussion section of Key Question 1 as recommended.
Discussion	I believe the Key Questions focusing on Harms could be combined. Avoiding the…	This comment was truncated and thus cannot be addressed.

Section	Comment	Response
Discussion	The Hispanic or Latino population is an ethnic group that has not been genetically well characterized. Perhaps the decision should be to study different genetic groups and move away from less clearly defined racial/ethnic determinations. Also additional research is needed on all non-Caucasian groups at present.	Thank you for this insightful comment. We have added text to the discussion section following Key Question 7 to reflect this recommendation.
Discussion	In the text, Asians (in addition to Latinos, African Americans) should be included in the "Future Research" sections. Also, certain Asian ethnic groups tend to have differences in BMI (Southeast, East, etc.).	The need for further information in Asians has been added to the Future Research section as recommended.
Figures	Figures 5 to 20 These trials had different follow-up times and this should be mentioned as one of the limitation of combining these studies	Text has been added to the discussion section following Key Question 1 regarding differences in the duration of follow-up amongst the included studies.
Tables	The executive summary contains many seemingly contradictory conclusions. For example, on page ES-3 the report states "ACE inhibitor or ARB therapy is better than placebo…" while later in the same cell, it states "ARB therapy (telmisartan) is similar to placebo…" Such discrepancies occur throughout the executive summary, and seem to be the result of the sequence of the analyses conducted for each comparison. The EPC first looks at the universe of studies of ACE inhibitors and ARBs before assessing the two drug classes individually and then comparing them. This approach is not logically consistent. One cannot assume that two different classes of drug are interchangeable, thus justifying combining them into a single meta-analysis, in the context of a Key Question that compares the two classes. That is, one cannot assume they are the same while simultaneously asking whether they are different. We strongly suggest that the EPC eliminate those analyses in which studies of ACE inhibitors and ARBs are combined to produce a single effect size. We recognize that this change would lead to a loss of statistical power, lowering the strength of evidence supporting many of the conclusions, but a conclusion based on unsound assumptions has no strength at all. If the EPC declines to revise methodological approach, it should, at the very least, insert an explanation into the executive summary justifying it and making it transparent.	We personally believe that providing an initial analysis with both ACE inhibitors and ARBs and then providing them with each drug class separately is the right approach to take. Let us try and present our rationale. From the clinician and healthcare decision maker perspective, there is great interest in whether renin- angiotensin- aldosterone system (RAAS) antagonists provide benefits and there are only two RAAS antagonistic drug classes that have evaluated these effects in this population (ACE inhibitors and ARBs). This is similar to evaluating antiepileptic agents together even though they represent numerous individual drug classes. Our point is not that one approach is inherently better than another but that this provides the greatest amount of transparency and people can view and use the analyses that best meet their needs. If a reader is more interested in either class alone, they have base case analyses for each class separately with which to base their decisions. So while we understand the trepidation of the public comment reviewer, we feel we would be remiss if we did not provide the information for the sake of the clinicians and healthcare decision makers who would like to see this information. We decided on this approach a priori and would certainly not want to make post-hoc decisions for something that is not clearly incorrect. The TEP and other reviewers of our CER also agree that this is a reasonable approach. In our revised CER we now provide more insight into our rationale for conducting the analyses in this way.

Section	Comment	Response
Tables	Table 13: Fosinipril was singled out as being similar to placebo in patients with IHD equivalent. This is based on a 400 patient RCT which included only dialysis patient. These patients are high risk anyway and thus data from this small trial may not be conclusive. I agree that the evidence is low. However, I recommend removing it from the final conclusion table.	We feel that including this data into both Table A as well as Table 13 increases the transparency of our results. We agree that the data is very weak for that outcome which is reflected in its strength of evidence rating. For clinicians, we feel that providing the available evidence and then rating its strength provides more useful information for decisionmakers than no comment on the topic area. Thus we feel that, to be inclusive, the information should remain in the table.
Tables	Table 13: CV mortality. The authors concluded that ACEI did not reduce CV mortality. While this may be accurate, data from other meta analysis have shown otherwise when combing these studies with other recent revascularization studies. There is however a very strong trend towards benefit. Since the lack of evidence does not mean lack of effect, I recommend changing this to state that the data is not conclusive and there is a hint that there might be benefit.	Thank you for this comment. The prior mentioned meta-analysis differs from our report in several notable ways. First, data from the TRANSCEND trial, which was included in our analysis, was not available at the time of the prior review. Additionally, the prior review included trials of patients immediately following revascularization. As we have discussed in our review, these trials were not be combined with trials such as HOPE and EUROPA due to differences in their study design. Our subgroup analysis evaluating ACE inhibitors alone provides data very similar to that of the prior paper, mainly due to the lack of including TRANSCEND (ARB data).
Tables	In the tables highlighting serum creatinine levels, for values expressed in units of mol/L or umol/L, it would be preferred to have the corresponding mg/dl value in parentheses (U.S. uses this unit).	The values in the corresponding tables have been changed to reflect units more commonly used in the United States.
Tables	For table 28 (hyperkalemia table): some mention of confounders (use of potassium-aparing diuretics, spironolactone/eplerenone, NSAIDs, beta-blockers, TMP/SMX, heparin, acidosis, etc.) should be made. In addition, the doses of the ACE Is/ARBs should be included in this table.	Thank you for this recommendation. We have added text to the discussion section following Key Question 4 to address the potential effects of confounders on the incidence of hyperkalemia. In addition, target doses for each agent have been added to the table, as suggested here and below.
References	No comments submitted.	
General	In the various discussion sections, the EPC frequently makes explicit treatment recommendations. For example, on page ES-13, the executive summary states that ACE inhibitors "should be used preferentially over ARBs." This contradicts AHRQ's statement that "The information in this report is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment." At one time, AHRQ policy prohibited explicit treatment recommendations in their health technology assessments. Has this policy changed?	Thank you for this comment. We have carefully reviewed our CER report and removed recommendations regarding preferential treatments.

Section	Comment	Response
General	In making explicit treatment recommendations, the EPC is actively practicing medicine. In so doing, we believe that the EPC is exceeding their mandate. The EPC may state that patients receiving Treatment A experience more favorable outcomes than those receiving Treatment B, or that the evidence in favor of Treatment A is stronger than evidence in favor of Treatment B. However, we firmly believe that it is not the role of the EPC, or of AHRQ, to say that Treatment A should be used preferentially over Treatment B. That decision should be left to the individual clinician. We urgently request that the EPC revise its statements throughout the document to avoid explicit treatment recommendations.	Thank you for this comment. We have carefully reviewed our CER report and removed recommendations regarding preferential treatments.
General	Comment: On behalf of Novartis Pharmaceuticals Corporation (Novartis), we are pleased to provide comments on the Draft Comparative Effectiveness Review entitled Comparative Effectiveness of Medical Therapies With or Without ACE Inhibitors or ARBs for Stable Ischemic Heart Disease. We would like to congratulate the investigators for conducting a thorough and insightful analysis of the literature and for developing a high-quality report. Addressing the comparative effectiveness of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for the treatment of ischemic heart disease has the potential to improve the quality of health care services by helping health care decision makers make well-informed choices among treatment alternatives.	Thank you, we tried to put together a CER that was informative and transparent.
General	There are times when the authors analyze the data assuming ACEs and ARBs ought to be combined and also times when ACE data and ARB data are presented separately. I'm glad the authors present the data both ways, but I'm vary wary of statements such as "indirect evidence suggests that subjects derived more benefits from ACE-I than ARB therapy for….". Such statements appear to be based on the authors qualitatively comparing the odds ratio for ACE vs. placebo and ARB vs. placebo and inferring substantive differences. In several instances, this is based on very few studies (or only one ARB study). I would advise against this, particularly since the direct comparison studies do not support this (including the very large ONTARGET included in this review). It may be feasible to combine studies across indications to see if there is a statistically significant difference in effect sizes for ACEs compared to ARBs, however, even so, I would be wary in the absence of data involving direct comparisons.	Thank you for this comment. Statements regarding indirect comparisons between ACE inhibitors and ARBs have been altered throughout the review as recommended.

Section	Comment	Response
General	The results from Key question 1 and 3 are different. When would a post revascularization patient become eligible to be included in the first group of studies? This is important because while it is not helpful to start patients on ACEI/ARB soon after revascularization, it will be helpful to know starting it result in a benefit. This could be estimated by looking at the exclusion criteria from HOPE, PEACE and EUROPA studies.	Thank you for this very insightful comment. We have added text to the discussion section following Key Question 3 to address the differences in the initiation of therapies between studies included in Key Question 1 and Key Question 3. It seems like beginning an ACE inhibitor or ARB 3-6 months following a revascularization procedure and then continuing this therapy over the long run may provide the optimal clinical benefit, however future studies are required to better help answer this question.
General	Page 40 of text: need to specify different dosing regiments of ACEIs such as fosinopril, ramipril, etc. for the different indications. The initial and target doses vary for each drug, depending on whether it is used for HTN, HF, or left ventricular dysfunction post-MI. For telmisartan, check if the maximum dose is 80 mg or 160 mg.	A table has been added to provide information from each study regarding both the initial dosing scheme as well as the target dose for each arm of the studies.
Appendix	Appendix C tables: for all tables, please include the target dose for the drugs featured in the column, "group".	Thank you for this recommendation. Target doses have been added for each table in Appendix C.