Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension – An Update of the 2007 Report*

Draft review available for public comment from October 22, 2010 to November 16, 2010.

Research Review Citation: Sanders GD, Coeytaux R, Dolor RJ, Hasselblad V, Patel UD, Powers B, Yancy WS Jr., Gray RN, Irvine RJ, Kendrick A. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension – An Update of the 2007 Report. Comparative Effectiveness Review No. #34. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-02-0025.) Rockville, MD: Agency for Healthcare Research and Quality. June 2011. 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. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Section	Comment	Response
Executive Summary	Current prescribing information is provided for the following four (4) products. Atacand(candesartan cilexetil) Tablets Atacand HCT (candesartan cilexetilhydrochlorothiazide)Tablets Zestril (lisinopril) Tablets Zestoretic(lisinopril and hydrochlorothiazide) Tablets.	Thank you for submitting this material.
Executive Summary	There is an incorrect description of the Renin-Angiotensin Aldosterone System (RAAS) on Page 8 (Executive Summary) Last 2 lines, starting with "Via proteolytic...". This appears to be a transcription error from the main report (Page 16, 3rd paragraph starting with, 'Via proteolytic...') which correctly describes the RAAS.	The description has been corrected and now matches the main report.
Introduction	The introduction identifies what was intended and why it is important to evaluate this topic area.	Thank you.
Introduction (Pg. 17)	In the last paragraph: Perhaps mention as an additional difference between ARBs and the other two classes that ARBs are selective for the AT1 receptor over the other angiotensin receptors.	This additional difference is now noted in the Introduction as well as the rise in plasma renin activity that occurs in ACEI and ARB treatment, but not direct renin inhibitors.
Introduction	This section clearly and succinctly summarizes the major issues and sets the stage for the subsequent key questions and finding.	Thank you.
Introduction	Pg. 17, lines 18-21: Awareness, treatment and control data are old and need to be updated.	These data have been updated with the recent NHANES report from Egan et al. in JAMA, 2010.
Introduction	Pg. 18, lines 21-25: same as above – references #8 & #9 are old.	We feel that reference #9 is still the most relevant reference for this section, but have updated reference #8 to reflect more recent analyses
Introduction	The attached information is supplied in response to an open public comment period. These materials may include information that is not found in the currently approved prescribing information for: • ATACAND® (candesartan cilexetil) Tablets • ATACAND HCT® (candesartan cilexetil-hydrocholrothiazide) Tablets • ZESTRIL® (lisinopril) Tablets • ZESTORETIC® (lisinopril and hydrochlorothiazide) Tablets The enclosed information is intended to provide pertinent data as part of the public comment opportunity and should in no way be construed as a recommendation for the use of these products in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for the above cited drugs. Prescribing information for these drugs may be obtained from www.astrazeneca-us.com or by calling the Information Center at AstraZeneca at 1-800-236-9933.	Thank you for submitting this material.
Introduction	Table 1, pg 23, Candesartan, col 2.	Update has been made.

	Please replace first bullet with "Elimination half-life is approximately 9 hr" to be consistent with the prescribing information. See ATACAND Prescribing Information section 12.3 Table 1	
Introduction	pg 23, Candesartan, col 3. The indication in Table 1, page 23, Candesartan, column 3 for heart failure is incomplete. Please add, "… reduce cardiovascular death and to reduce heart failure hospitalizations" to be consistent with the approved prescribing information See ATACAND Prescribing information section 1.2. Table 1,	Update has been made.
Introduction	pg 23, col 4. The recommended dosing for heart failure was omitted from Table 1, column 4. Please consider adding the following: The recommended initial dose for treating heart failure is 4 mg once daily. The target dose is 32 mg once daily, which is achieved by doubling the dose at approximately 2-week intervals, as tolerated by the patient. See ATACAND Prescribing Information section 2.3. Table 1	Update not made, as this column only contains dosing information for treating hypertension.
Introduction	pg 23, col 5. First bullet regarding pregnancy risk appears to have been copied from an ACE-Inhibitor entry. Recommend the following language: "When used in pregnancy during the second and third trimesters, drugs that act directly on the renin angiotensin system can cause injury and even death to the developing fetus." See ATACAND Prescribing Information, Boxed Warning	Table 1 has been revised to reflect the suggested wording.
Methods	The methods are generally appropriate.	Thank you.
Methods	I am concerned about interpreting 'long term' as '12 weeks or longer.' This would be appropriate for blood pressure control and perhaps for adherence to medication and common adverse events. It is nowhere near long enough to assess diabetes, cardiovascular events or mortality. I don't know whether it is reasonable for assessing kidney disease or LV function, but I would be dubious.	We agree. Some of our outcomes of interest, such as blood pressure lowering or medication side effects, could be reasonably assessed in a short timeframe, while many others (e.g. persistence, mortality, morbidity) may require years of follow up. To include a broad range of studies reporting on our multiple outcomes, we opted to include studies with a minimum of 12 weeks follow up with the understanding that many of our outcomes would only be reported in studies of longer duration. This has been clarified in the methods describing this decision
Methods	Something should be said somewhere about the recent report on higher cancer rates with ARBs vs ACE clinical trials [The Lancet Oncology, Volume 11, Issue 7, Pages 627-636. July 2010 doi:10.1016/S1470-2045(10)70106-6]. As it stands, it's not clear whether it was just the timing that left it out or whether there was a deliberate choice.	We added a paragraph commenting on this systematic review and its importance for future research in the "Future Research" section. This outcome was not reported in any of our other studies and we are not able to provide further evidence on this outcome.

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Methods	The inclusion and exclusion criteria are clearly stated, with extensive appendices describing the search strategy used and sources examined. Unlike Cochrane reviews, the authors included evidence from both RCTs and observational studies, which adds greatly to the body of evidence considered and also allows "effectiveness" conclusions beyond "efficacy" alone.	Thank you.
Methods	Consider more discussion on the potential for bias in the included observational studies. For example, many patients in typical clinical settings are first tried on ACE inhibitors and then switched to ARBs if intolerant. Such unidirectional switchers are likely to affect conclusions for almost all of the included observational data, and warrants further discussion on the implications related to changes in patient adherence, rates of switchers, selection bias, confounding, etc.	We have added a paragraph in the Methods section under "Applicability" outlining the advantages of including observational studies, the risk for bias from including them, and how we addressed this in the analysis phase by presenting separate meta-analysis for RCTs and observational studies.
Methods	Several meta-analyses were conducted and reporting of these should all adhere to the PRISMA statement (see http://www.prisma-statement.org/).	We now clarify our additional details in our data synthesis methodology section detailing adherence the PRISMA statement
Methods	The potential for publication bias should be assessed and reported (likely in an Appendix) for all meta-analyses conducted.	As suggested we now include Appendix H, which discusses the potential for publication bias for the meta analyses with sufficient studies.
Methods	Pg. 29: What is gray (grey?) literature?	We now include a definition of gray literature for the reader.
Methods	Pgs. 31 & 32: Analytic framework is described nicely.	Thank you.
Results	The results are appropriate and presented clearly, apart from the comment about forest plot labeling made below.	As described below we have now clarified the forest plot labeling.
Results	A good practice followed by the authors was to report both absolute and relative effect sizes. For example, when reporting an Odds Ratio (a relative measure), the authors also searched for the best available absolute measure to provide context. This is laudable. Figure 4 on pg. 49 is the exception, where a 26% larger odds is reported but this is not made clinically meaningful. Furthermore, focusing on statistical significance as in this example distracts from the more important question of whether this is clinically significant/relevant.	We have now added in additional text to this section discussing the potential clinical significance of this finding
Results	Figure 3 does not live up to the standard of other meta-analysis figures. Specifically, the combined estimate is missing its label, Favors A vs B should be replaced with Favors ACE or ARB (as in Figure 4; also missing in Figure 5 and others in the report), the studies should be ordered in a meaningful way (e.g., all the RCTs together, all the observational studies together, and then sorted by year or study size), and the corresponding table 6 should list the studies in the same (revised) order.	We have re-formatted the figures and tables to list RCTs and observational studies together in a group and then by year.
Results	Furthermore, all the meta-analysis figures do not need z-value or p-	The meta-analysis figures have been

	values reported as those can be derived (if needed) from the 95% CIs already reported.	simplified and no longer include z or p values
Results	Page 57: when using SMDs for meta-analysis, it is important to translate the final result back into clinically meaningful measures, otherwise we are left wondering if the statistical significance matters.	We now include additional explanation about standardized mean difference and its use in the meta-analysis
Results	Page 59, line 54: should it be p>0.05, or is the point that everything was so insignificant at the p>0.50 level?	Yes, the p>0.5 is to indicate that there is no significant difference between the two groups discussed
Results	Please see comment above re: ONTARGET.	See under "General" comments.
Results	"Morality" on Pg. 44, line 8 should be "mortality.	This error has been corrected
Results	Pg 43, para 1, sentence 2. "morality" should be replaced by "mortality"	This error has been corrected
Results	Pg 49, table 8, Derosa 2003, col 3. Unable to verify from the publication that study population consisted of 100% white patients.	The race/ethnicity information for the Derosa article has been removed
Results	Pg 49, table 8, Derosa 2003, col 6. Table 8, column 6 reports "NR" regarding "?TC," however the publication reports TC mg/dL [-1 (0.4)] for candesartan and [- 12(5.6)] for perindopril at 12 weeks of treatment. See DeRosa 2003, Table II.	Table 8 column 6 has been corrected
Results	Pg 49, table 8, Derosa 2003, cols 7-9. Table 8 reports changes as percent, but the publication reports the values as mg/dL. Recommend that Table 8 report the values as mg/dL.	The Table has been corrected to now report the values as mg/dL.
Results	Pg 50, para 3, sentence 3-5. Sentence 3-5, page 50, paragraph 3 refers to DeRosa et al (ref 1) and changes in glucose. As glucose was measured on several occasions, recommend indicating that this measurement was after 12 months of treatment.	We have added in additional text indicating the measurement was after 12 months.
Results	Pg 74, para 2, sentence 6. Page 74, paragraph 2, sentence 6 refers to DeRosa et al (ref 1) and changes in glucose. As glucose was measured on several occasions, recommend indicating that this measurement was after 12 months of treatment.	We have added in additional text indicating the measurement was after 12 months.
Results	Pg 59, KQ 2, Bullet 4. Key conclusions for KQ2, bullet 4 currently reads: "Angioedema was not reported in the majority of studies, making it impossible to accurately characterize its frequency and timing in this population. In the studies that did report episodes of angioedema, this adverse event was observed only in patients treated with an ACEI or a direct renin inhibitor." We would like to suggest that the researchers consider consulting other data sources such as adverse event data bases (E.G., the FDA AERs database) for information on angioedema. Conceivably, information from adverse event databases would support the clinical impression that the risk for angioedema is	We have noted in our discussion of angioedema that its reported frequency has been much greater in ACEI than ARBs. We have not changed the bullets of our key points because our review was not able to provide further evidence on the relative frequency of this rare side effect.

	quantitatively greater for ACE inhibitors than for ARBs and that these data are pertinent to the potential users of the AHRQ document. This is particularly important in that angioedema can prove fatal, particularly among African Americans and the uninsured, who may be treated and released from hospital emergency rooms rather than be hospitalized in appropriate care units.	
Results	Pg 59, Key Question 2. For Results Key Question 2, safety information, please note that ACE inhibitors pose unique, albeit rare, interaction risks not seen with ARBs. These are described in the full prescribing information for ZESTRIL and below. Anaphylactoid Reactions During Membrane Exposure: Sudden and potentially life threatening anaphylactoid reactions have been reported in some patients dialyzed high-flux membranes (e.g., AN69®) and treated concomitantly with an ACE inhibitor. In such patients, dialysis should be stopped immediately, and aggressive therapy for anaplylactoied reactions must be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be give to using a different type of dialysis membrane or a different class of antihypertensive agent. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulphate absorption. Gold: Nitritoid reactions (symptoms including facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ZESTRIL.	The purpose of this section is to describe the potential adverse events that may be encountered in the typical hypertensive patient taking these medications and that are reported in our included studies. The extremely rare events described by the reviewer all represent putative interactions that are beyond the scope of this review.
Summary and Discussion	Even though it was not originally thought of with this evaluation, whether ARBs negatively impact the risk of cancer is currently a hot topic that is too late to include in the body of the report but would be a future area of research.	We agree and have added text under KQ2 and have listed this important outcome in the future research section.
Summary and Discussion	I don't think that the evidence on mortality is better than "insufficient," and the discussion on pp. 43-44 seems to agree.	We have re-reviewed the evidence and believe that although there are several issues with the evidence base on mortality, the 21 studies do justify a rating of "low"
Summary and Discussion	The recommendations for future research appropriately include longer-term studies. They should also include studies that can meaningfully examine cardiovascular/cerebrovascular event rates, at least to rule out the possibility that ARBs or renin inhibitors are substantially less effective.	We have added this in the future research section
Summary and Discussion	Some sort of followup of the recent report of higher cancer risk with ARBs is also needed – it is quite likely to be a false positive, but it would be important to try to find out.	We agree and have responded as noted above.
Summary	The GRADE table (pg. 78) is a welcome summary item, but requires	We now include descriptions of these

and Discussion	some explanation. For example, what does the "consistency" column mean? Rather than having readers find the original GRADE papers, a very brief description of the relevant definitions would be appreciated.	columns in the legend of the table.
Summary and Discussion	The GRADE balance sheet (pg. 81) should include absolute measures, not just the relative measures (odds ratios).	Given the event rates and outcomes presented in the table we felt that the odds ratios were the more informative information to present in this summary table.
Summary and Discussion	In tables 28 & 29, it is unclear what the "-" represent. Is that no data? Not relevant? Negative association?	In these tables "-" represents no relevant data. This has been clarified in the table legends.
Summary and Discussion	In the "Future Research" section it is unclear how these were derived. While the methods used to arrive at all prior results and conclusions are extensively documented, this section seems quite subjective and potentially controversial. For example, on Pg. 83, a recommendation is made for "Evaluation of specific pairs of ACEIs and ARBs to allow differentiation within class." Why is this important? One might argue that since 70%+ of patients on ACE inhibitors are on lisinopril (unpublished data), comparative effectiveness research on lisinopril should be prioritized.	The future research section is based on the investigator's read of the existing evidence and feedback from our technical expert panel. Following the publication of this report we will be developing a "future research needs" report identifying and prioritizing future research studies in this domain and we will develop this section further at that time.
Summary and Discussion	Fine… no problems.	Thank you.
General (quality)	Quality of the report is good.	Thank you.
General (quality)	Quality of the report is good.	Thank you.
General (quality)	Quality of the report is superior.	Thank you.
General (quality)	Quality of the report is superior.	Thank you.
General (clarity and usability)	Yes, the report is well structured and the conclusions concerning a lack of difference between classes except for cough is informative for clinicians and health policy decision makers.	Thank you.
General	The population and audience are defined. The key questions are appropriate and explicitly stated	Thank you.
General (clarity and usability)	The forest plots of meta-analyses would be more usable if they were labeled, e.g., "favors ACEI" and "favors ARB" rather than "favors A" and "favors B."	The figures have been modified to include more informative labels
General (clarity and usability)	The report is well-structured and organized. The main problem with using the conclusions to inform policy or practice decisions is that the evidence is not very strong on important questions.	We agree that there are gaps in the evidence and that there are several areas of future research that should be prioritized to help fill these gaps

General	This report is an invaluable update to an important report only a few years old, yet already out-of-date. The information it provides is directly applicable to clinical practice, and is presented in a meaningful and user-friendly way. The target population and audience are clearly defined, and the key questions are appropriate and explicit. In light of upcoming revisions to national guidelines (e.g. JNC 8 for hypertension is forthcoming) – this report is particularly timely and will inform that process.	Thank you.
General (clarity and usability)	The report is well structured and organized. The tables and figures are appropriately placed in the text so readers don't have to flip back and forth from the text, and most labels are clear (except for Pg. 78, Table 28, where SD, SA, DR, PC are used as column headings and not explained until Pg. 80).	We have moved reformatted Table 28 so that the footnotes appear beginning on the first page of the table.
General (clarity and usability)	The four areas of research prioritized (pg. 83) seem a bit arbitrary. For example, angioedema is important, but how many deaths attributable to it can actually be found yearly, relative to the new sum of disability attributable to non-adherence? Pg. 83, line 41 – research on cough/quality of life. Why is this important? Most patients are quick to complain about persistent cough and are quickly switched to ARBs, limiting the effect on "quality of life." For the majority of the report, however, the Key Questions are answered in ways that can inform policy and practice, and this is the major contribution to the literature.	We agree that the impact of cough on quality of life is likely to be modest over the long term and have deleted that point. We have added cancer risk as an important area of future research and reordered the remaining items, with the comment on angioedema last.
General	Yes on all counts. My only major question is why ONTARGET was not cited… it is the only major RCT that compared an ACEI and ARB head to head and had hard outcomes.	We agree that ONTARGET was an important direct comparison study; unfortunately it did not meet our specified inclusion criteria of reporting results for patients with hypertension. We have commented in the future research section that combining studies across target conditions may be an important strategy for future reviews so that studies like ONTARGET can be combined with our included studies.
General	Pg. 10, lines 28-30: It is inappropriate to postulate that DRIs may have more favorable side effect profiles and efficacy than ACEIs or ARBs – they may have more side effects and less efficacy.	We agree and have modified this to indicate that their comparative efficacy and side-effects are not well known.
General (clarity and usability)	Yes on all counts.	Thank you.
General (clarity and usability)	For the cancer study, compare the included studies to those included in your report. Aside from the risk itself, the emergence of a new adverse event from an outside meta-analysis raises the question of	We have added additional information on the systematic review reporting cancer risk. In addition, we have commented on study

	the strategy used in an EPC report regarding harms. An indiosyncratic signal (cancer) is by definition clearly relevant to any subpopulation (such as patients with hypertension). The question is whether by excluding whatever trial had the original clue, we missed the clue; and by then restricting the review to studies of a particular population, we missed the signal.	selection for future research. Most reviews focus on the target condition for inclusion (i.e. hypertension, ischemic heart disease, etc); however future systematic reviews focused on particular outcomes, but with greater leniency in the target conditions included may yield important new information.
General (clarity and usability)	Regarding ONTARGET, if its omission puzzles reviewers, it will puzzle others as well. From the call the authors' answers are (1) it was addressed thoroughly in another report, to which the reader should be referred (2) you looked at it again to see if it had any particular relevance to patients with essential hypertension. With respect to benefits, they didn't report results for that subgroup. With respect to adverse events, an important finding of ONTARGET is that combination therapy had higher adverse event rates but no more benefit than a single drug. Does this finding emerge in the literature on HTN? Wouldn't a reasonable person find it relevant, either as the closest thing to the desired evidence (not exactly the right population, but well-done comparison study) or as validation (if combo therapy has more harms in some HTN trials, it ought to have more harms in patients with ischemic heart disease risk factors, too--and it does.) In other words, inclusion strategies must be aligned with and take their lead from what a reasonable patient or clinician would like to know.	We agree. Prior systematic reviews of ACEI vs. ARBs have limited inclusion of studies to those conducted in patients with the target condition at the time of enrollment (i.e. hypertension, ischemic heart disease, congestive heart failure, or nephropathy); however all have examined an overlapping set of efficacy and safety outcomes. As a result, important direct comparison trials are often excluded from reviews such as ours because they don't meet the target condition inclusion criteria. Such was the case of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), which was excluded from this review because no results were reported exclusively for patients with hypertension. It is likely that combining studies reporting identical outcomes, but in different target populations, may yield important new information, particularly for rarer events, not contained in any of the individual reviews. This text has been added to our future research section.
General (study inclusion)	OMISSION OF STUDIES RELATED TO THE ONGOING TELMISARTAN ALONE AND IN COMBINATION WITH RAMIPRIL GLOBAL ENDPOINT TRIAL (ONTARGET) The landmark ONTARGET trial published in 2008 [1], the largest of its kind ever conducted, looked at cardiovascular outcomes between telmisartan, ramipril, and the combination of both telmisartan and ramipril. The study found that telmisartan alone was non-inferior to ramipril alone for the combined endpoint of; death from cardiovascular causes, myocardial infarction, stroke, and hospitalization for heart failure; however, telmisartan did have lower rates of angioedema and cough. In light of AHRQ's key questions,	We agree – as noted in response to other reviewers raising this issue.

	this trial may be important for inclusion. The key questions 1 and 2 specifically examine cardiovascular events and adverse events between drug classes. Therefore, based on the outcomes of interest defined in the report, this would seem to be an important study for inclusion, especially in light of the fact that it is the only study comparing ACEi and ARBs in a blinded head to head fashion. Therefore, we recommend that AHRQ consider including the ONTARGET data for the reasons outlined above.	
General (study inclusion)	The report does state that there are several reasons by which a study may be excluded, and references that these exclusion criteria are outlined in Appendix C. However, Appendix C is not available in the published draft report. Additionally, the list of excluded studies is referenced to be included in Appendix G, but once again this Appendix G is not available with the draft report. In addition, we would recommend AHRQ publish the relevant referenced Appendices in the draft report in order for stakeholders to clearly understand why a particular article was not included and incorporate that into the commenting process.	We apologize that the appendices were not easily accessible through the AHRQ website during the public review process—they should have been available for reviewers.
General (study methodology)	STUDY METHODOLOGY: DISPARITY IN ODDS RATIOS USED IN 2007 REPORT AND 2010 UPDATE From our review of the draft report, the methodology used between the 2007 and 2010 reports appear to be similar. However, we noted that the 2010 AHRQ report uses a different approach in presenting odds ratios (OR). The 2007 report refers to Peto ORs whereas the 2010 report uses the more traditional Mantel-Haenszel ORs for each study. We note that Peto ORs are often used in cases where reporting small differences may be significant, such as in large trials. Additionally, the Peto method can be more useful when there are many trials that have no events occur in one or both arms. We believe it would be helpful to understand the reasoning for this change in OR reporting (e.g. the new data included in the 2010 update influenced changing to using the traditional method of OR reporting). We urge AHRQ to comment on why they chose to change the type of OR reported, despite including many of the same studies from the 2007 report, thereby clearly demonstrating and explaining that these are different types of ORs.	In general, we used random-effects models (empirical Bayes or DerSimonian & Laird). Random-effects models have the advantage that they reduce to the fixed-effect models when there is no heterogeneity. However, several of our meta-analyses were done across very heterogeneous studies, and Peto's method is not appropriate in that situation. In addition, Peto's method is known to be very biased when the estimated ORs are not near 1.
General (evidence gaps/future research)	EVIDENCE GAPS AND FUTURE RESEARCH The updated report appropriately states that there remain several evidence gaps in the ability to determine whether or not there are clinically meaningful differences in long-term outcomes in individuals	We have included a statement of future research that explores the identification of unique effects of specific agents that are not shared by other members of their respective drug class.

	with essential hypertension. We agree that further research is needed to determine whether or not there are true differences within the ACEI and ARB therapeutic classes. Consideration of drug specific characteristics such as variations in tissue specificity, side effect profiles, and methods of metabolism and excretion may be important factors in choosing the appropriate drug regimen for an individual patient. However, research does exist that demonstrates that both losartan and valsartan lower the incidence of new onset Type II diabetes for patients on these medications [2,3]. This result can be considered clinically relevant for these specific ARBs and should be considered when comparing them to ACEIs. Additionally, many researchers and clinicians have highlighted the concept of "class effects", specifically related to ACEIs and ARBs, discussing that mechanism of action, safety profiles [4], and varying degrees of beneficial effects [5] may play a significant role in efficacy for given patient populations. Such literature underscores the notion that "class effect" may not occur consistently and that individual treatments have potentially significant differences. Furthermore, we note that the report introduces some of the pharmacological differences between drug classes. However, there may be other key pharmacological differences between the different classes that may lead to clinically relevant treatment effect differences across various patient populations. For instance, literature suggests that both ARBs and ACEIs may provide similar cardiovascular protective effects though side effect profiles differ significantly making one option more appealing to patients than the alternative [6]. We encourage AHRQ to include this as a potential area of future research to help tailor effective clinical care for specific patient populations based on individual characteristics.	
General (evidence gaps/future research)	References: [1] The ONTARGET Investigators. "Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events". NEJM. 2008. 358;15:1547-1559. [2] The VALUE Trial Group. "Outcomes in Hypertensive Patients at High Cardiovascular Risk Treated with Regimens Based on Valsartan or Amlodipine: the VALUE Randomised Trial". Lancet. 2004;363:2022- 31. [3] The LIFE Study Group. "Cardiovascular Morbidity and Mortality in the Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE): A Randomized Trial Against Atenelol. Lancet.2002;359:995-1003. [4] Furberg C and Pitt B. "Are All Angiotensinconverting Enzyme Inhibitors Interchangeable?". J Am Coll Cardiol. 2001;37:1456-1460. [5] Miura S, Karnik S, and Saku K. "Angiotensin II Type 1 Receptor: Class Effects versus Molecular Effects. J Renin Angiotensin	The relevant references are included in the updated report

	Aldosterone Syst. Published online July 5, 2010. [6] Toth P. "Pleiotropic Effects of Angiotensin Receptor Blockers: Addressing Comorbidities by Optimizing Hypertension Therapy." J Clin Hypertens. Published online October 5, 2010.	
General	In conclusion, we look forward to working together to maximize the value of this and future reports for all relevant stakeholders, especially as new evidence is generated and new treatment options for hypertension are developed. We underscore the importance of updating any corollary materials (e.g., patient guides) in order to reflect the updated review. As BIPI's own research and development in this therapeutic area continues, we will work to ensure that AHRQ has the most robust information to appropriately capture and interpret the body of clinical evidence on oral medications for hypertension.	Thank you. We agree that it will be important to update the corollary materials you mention to reflect the content of the updated review.
General (technical problem submitting comments documents)	References package inserts are not loading. Will submit or send hard copy prior to the deadline.	We reported the technical problem you experienced when trying to submit documents along with your comments to AHRQ. Thank you for reporting this.